

FORM PTO-1590 (REV. 10-96)		U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER 48962-A-PCT-US/JPW/KJR
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371			U.S. APPLICATION NO. (If known, see 37 CFR 1.5) 09/230111
INTERNATIONAL APPLICATION NO PCT/US97/12677	INTERNATIONAL FILING DATE July 18, 1997	PRIORITY DATE CLAIMED July 22, 1996	
TITLE OF INVENTION COMPOUNDS THAT INHIBIT THE INTERACTION BETWEEN SIGNAL-TRANSDUCING PROTEINS AND THE GLGF (PDZ/DHR) DOMAIN AND USES THEREOF			
APPLICANT(S) FOR DO/EO/US Taka-Aki Sato and Junn Yanagisawa			
Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:			
<ol style="list-style-type: none">1. <input checked="" type="checkbox"/> This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.2. <input type="checkbox"/> This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.3. <input type="checkbox"/> This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).4. <input checked="" type="checkbox"/> A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.5. <input checked="" type="checkbox"/> A copy of the International Application as filed (35 U.S.C. 371(c)(2))<ol style="list-style-type: none">a. <input type="checkbox"/> is transmitted herewith (required only if not transmitted by the International Bureau).b. <input type="checkbox"/> has been transmitted by the International Bureau.c. <input checked="" type="checkbox"/> is not required, as the application was filed in the United States Receiving Office (RO/US).6. <input type="checkbox"/> A translation of the International Application into English (35 U.S.C. 371(c)(2)).7. <input checked="" type="checkbox"/> Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))<ol style="list-style-type: none">a. <input type="checkbox"/> are transmitted herewith (required only if not transmitted by the International Bureau).b. <input type="checkbox"/> have been transmitted by the International Bureau.c. <input type="checkbox"/> have not been made; however, the time limit for making such amendments has NOT expired.d. <input checked="" type="checkbox"/> have not been made and will not be made.8. <input type="checkbox"/> A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).9. <input type="checkbox"/> An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).10. <input type="checkbox"/> A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).			
Items 11. to 16. below concern document(s) or information included:			
<ol style="list-style-type: none">11. <input type="checkbox"/> An Information Disclosure Statement under 37 CFR 1.97 and 1.98.12. <input type="checkbox"/> An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included13. <input checked="" type="checkbox"/> A FIRST preliminary amendment. <input type="checkbox"/> A SECOND or SUBSEQUENT preliminary amendment.14. <input type="checkbox"/> A substitute specification.15. <input type="checkbox"/> A change of power of attorney and/or address letter.16. <input type="checkbox"/> Other items or information: Express Mail Certificate of Mailing bearing Label No. EM 165 675 225 US dated January 22, 1999; a Computer Diskette containing "Sequence Listing"; a statement In Accordance With 37 C.F.R. §1.821(f); copy of Assignment submitted for recordation on August 27, 1998.			

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416 Rec'd PCT/PTO 22 JAN 1999

Dkt. 48962-A-PCT-US/JPW/KJR

IN THE UNITED STATES ELECTED OFFICE (EO/US)

Applicants : Taka-Aki Sato and Junn Yanagisawa
U.S. Serial No : Not Yet Known
(U.S. National Stage of
International Application No. PCT/US97/12677
filed 18 July 1997)
Filed : Herewith
For : COMPOUNDS THAT INHIBIT INTERACTION BETWEEN
SIGNAL-TRANSDUCING PROTEINS AND THE GLGF
(PDZ/DHR) DOMAIN AND USES THEREOF

1185 Avenue Of The Americas
New York, New York 10036
January 22, 1999

Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Attn.: EO/US

Sir:

PRELIMINARY AMENDMENT

Applicants request that the following amendments be made in the
above-identified application:

In the Specification:

On page 1, after the title, on line 7, please insert the
following new sentence:

--This application is a §371 of PCT International
Application No. PCT/US97/12677, filed July 18, 1997, which
claims priority of and is a continuation-in-part of U.S.
Serial No. 08/681,219, filed July 22, 1996, the contents of
which are hereby incorporated by reference in their
entirety into the present application.--

Taka-Aki Sato and Junn Yanagisawa
U.S. Serial No.: Not Yet Known
(U.S. National Stage of International
Application No. PCT/US97/12677 filed 18 July 1997)
Filed: Herewith
Page 2

In the claims:

Please cancel claims 1-26 and 77-120, without prejudice to applicants' right to pursue the subject matter of these claims in the future.

REMARKS

This application is a §371 of PCT International Application No. PCT/US97/12677, filed July 18, 1997, which claims priority of and is a continuation-in-part of U.S. Serial No. 08/681,219, filed July 22, 1996.

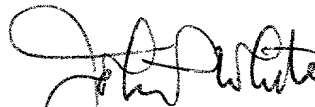
By this Amendment applicants have canceled claims 1-26 and 77-120 without prejudice to applicants' right to pursue the subject matter of these claims in a future continuation or divisional application or disclaimer. Accordingly, upon entry of this Amendment, claims 27-76 will be pending and under examination.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

Taka-Aki Sato and Junn Yanagisawa
U.S. Serial No.: Not Yet Known
(U.S. National Stage of International
Application No. PCT/US97/12677 filed 18 July 1997)
Filed: Herewith
Page 3

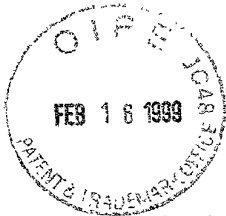
No fee is deemed necessary in connection with the filing of this Preliminary Amendment. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



John R. White
Registration No. 28,678
Attorney for Applicant
Cooper & Dunham LLP
1185 Ave of the Americas
New York, New York 10036
(212) 278-0400

Applicant or Patentee: Taka-Aki Satō and Junn Yanagisawa Attorney's 48962-A-PCT-
Serial or Patent No.: 09/230,111 Docket No: US/JPW/EMW
Filed or Issued: January 22, 1999
Title of Invention or Patent: COMPOUNDS THAT INHIBIT INTERACTION BETWEEN SIGNAL-
TRANSDUCING PROTEINS AND THE GLGF (PDZ/DHR) DOMAIN
AND USES THEREOF



VERIFIED STATEMENT (DECLARATION) CLAIMING
SMALL ENTITY STATUS UNDER 37 C.F.R. §1.9(f)
AND §1.27(d) - NONPROFIT ORGANIZATION

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

Name of Organization: The Trustees of Columbia University in the City of New York

Address of Organization: West 116th Street and Broadway
New York, New York 10027

TYPE OF ORGANIZATION:

☒ UNIVERSITY OR OTHER INSTITUTION OF HIGHER EDUCATION
☐ TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE 26 U.S.C. §§501(a) and 501(c)(3)
☐ NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA
NAME OF STATE: _____
CITATION OF STATUTE: _____
☐ WOULD QUALIFY AS TAX EXEMPT UNDER INTERNAL REVENUE SERVICE CODE 26 U.S.C. §§501(a) and 501(c)(3) IF LOCATED IN THE UNITED STATES OF AMERICA
☐ WOULD QUALIFY AS NONPROFIT SCIENTIFIC OR EDUCATIONAL UNDER STATUTE OF STATE OF THE UNITED STATES OF AMERICA IF LOCATED IN THE UNITED STATES OF AMERICA
NAME OF STATE: _____
CITATION OF STATUTE: _____

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 C.F.R. §1.9(e)* for purposes of paying reduced fees under 35 U.S.C. §41(a) and 41(b), with regard to the invention entitled COMPOUNDS THAT INHIBIT INTERACTION BETWEEN SIGNAL-TRANSDUCING PROTEINS AND THE GLGF (PDZ/DHR) DOMAIN AND USES THEREOF by inventor(s) Taka-Aki Sato and Junn Yanagisawa

described in:

☐ the specification filed herewith
☒ application serial no. 09/230,111 filed January 22, 1999
☐ patent no. _____ issued _____

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above identified invention.

If the rights held by the nonprofit organization are not exclusive each individual, concern, or organization known to have rights to the invention is listed below^a and no rights to the invention are held by any person, other than the inventor, who could not qualify as a small business concern under 37 C.F.R. §1.9(d)* or a nonprofit organization under 37 C.F.R. 1.9(e)*

^a NOTE: Separate verified statements are required from each person, concern, or organization having rights to the invention averring to their status as small entities. 37 C.F.R. §1.27.

Name: N/A
Address: _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

37 C.F.R. §§1.9(d), 1.9(e)

(d) A small business concern as used in this chapter means any business concern as defined by the Small Business Administration in 13 C.F.R. §121.3-18, published on September 30, 1982 at 47 FR 43273. For the convenience of the users of these regulations, that definition states:

§121.3-18 Definition of small business for paying reduced patent fees under Title 35, U.S. Code.

(a) Pursuant to Pub. L. 97-247, a small business concern for purposes of paying reduced fees under 35 U.S. Code 41(a) and (b) to the Patent and Trademark Office means any business concern (1) whose number of employees, including those of its affiliates, does not exceed 500 persons and (2) which has not assigned, granted, conveyed, or licensed, and is under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who could not be classified as an independent inventor if that person had made the invention, or to any concern which would not qualify as a small business concern or a nonprofit organization under this section. For the purpose of this section concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both. The number of employees of the business concern is the average over the fiscal year of the the persons employed during each of the pay periods of the fiscal year. Employees are those persons employed on a full-time, part-time or temporary basis during the previous fiscal year of the concern.

(b) If the Patent and Trademark Office determines that a concern is not eligible as a small business concern within this section, the concern shall have a right to appeal that determination to the Small Business Administration. The Patent and Trademark Office shall transmit its written decision and the pertinent size determination file to the SBA in the event of such adverse determination and size appeal. Such appeals by concerns should be submitted to the SBA at 1441 L Street, NW., Washington, D.C. 20416 (Attention: SBA Office of General Counsel). The appeal should state the basis upon which it is claimed that the Patent and Trademark Office initial size determination on the concern was in error; and the facts and arguments supporting the concern's claimed status as a small business concern under this section.

(e) A nonprofit organization as used in this chapter means (1) a university or other institution of higher education located in any country; (2) an organization of the type described in section 501(c)(3) of the Internal Revenue Code of 1954 (26 U.S.C. 501(c)(3)) and exempt from taxation under section 501(a) of the Internal Revenue Code (26 U.S.C. 501(a)); (3) any nonprofit scientific or educational organization qualified under a nonprofit organization statute of a state of this country (35 U.S.C. 201(i); or (4) any nonprofit organization located in a foreign country which would qualify as a nonprofit organization under paragraphs (e)(2) or (3) of this section if it were located in this country.

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. 37 C.F.R. §1.28(b)*.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Name of Person Signing: Mr. Jack M. Granowitz
Title In Organization: Executive Director, Columbia Innovation Enterprise
Address: Amsterdam & 120th Street - Suite 363 New York, New York 10027
Signature: *Jack M. Granowitz*
Date Of Signature: Feb 4, 1999

37 C.F.R. §1.28(b)

(b) Once status as a small entity has been established in an application or patent, fees as a small entity may thereafter be paid in that application or patent without regard to a change in status until the issue fee is due or any maintenance fee is due. Notification of any change in status resulting in loss of entitlement to small entity status must be filed in the application or patent prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate pursuant to §1.9 of this part. The notification of change in status may be signed by the applicant, any person authorized to sign on behalf of the assignee, or an attorney or agent of record or acting in a representative capacity pursuant to §1.34(a) of this part.

RECEIVED

09/230111

COMPOUNDS THAT INHIBIT INTERACTION BETWEEN SIGNAL-TRANSDUCING PROTEINS
AND THE GLGF (PDZ/DHR) DOMAIN AND USES THEREOF

5

The invention disclosed herein was made with Government support under Grant No. R01GM55147-01 from the National Institutes of Health of the United States Department of Health and Human Services. Accordingly, the U.S. Government has certain rights in this invention.

BACKGROUND

Throughout this application, various publications are referenced by author and date. Full citations for these publications may be found listed alphabetically at the end of the specification immediately preceding Sequence Listing and the claims. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the invention described and claimed herein.

Fas (APO-1/CD95) and its ligand have been identified as important signal-mediators of apoptosis (Itoh, et al. 1991) The structural organization of Fas (APO-1/CD95) has suggested that it is a member of the tumor necrosis factor receptor superfamily, which also includes the p75 nerve growth factor receptor (NGFR) (Johnson, et al. 1986), the T-cell-activation marker CD27 (Camerini, et al. 1991), the Hodgkin-lymphoma-associated antigen CD30 (Smith, et al. (1993), the human B cell antigen CD40 (Stamenkovic, et al. 1989), and T cell antigen OX40 (Mallett, et al. 1990). Genetic mutations of both Fas and its ligand have been associated with lymphoproliferative and autoimmune disorders in mice (Watanabe-Fukunaga, et al. 1992; Takahashi, et al. 1994).

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Furthermore, alterations of Fas expression level have been thought to lead to the induction of apoptosis in T-cells infected with human immunodeficiency virus (HIV) (Westendorp, et al. 1995).

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Several Fas-interacting signal transducing molecules, such as Fas-associated phosphatase-1 (FAP-1) (Figure 1) (Sato, et al. 1995) FADD/MORT1/CAP-1/CAP-2 (Chinnaiyan, et al. 1995; Boldin, et al. 1995; Kischkel, et al. 1995) and RIP (Stanger, et al. 1995), have been identified using yeast two-hybrid and biochemical approaches. All but FAP-1 associate with the functional cell death domain of Fas and overexpression of FADD/MORT1 or RIP induces apoptosis in cells transfected with these proteins. In contrast, FAP-1 is the only protein that associates with the negative regulatory domain (C-terminal 15 amino acids) (Ito, et al. 1993) of Fas and that inhibits Fas-induced apoptosis.

20 FAP-1 (PTPN13) has several alternatively-spliced forms that are identical to PTP-BAS/hPTP1E/PTPL1, (Maekawa, et al. 1994; Banville, et al. 1994; Saras, et al. 1994) and contains a membrane-binding region similar to those found in the cytoskeleton-associated proteins, ezrin, (Gould et al. 1989) radixin (Funayama et al. 1991) moesin (Lankes, et al. 1991), neurofibromatosis type II gene product (NFII) (Rouleau, et al. 1993), and protein 4.1 (Conboy, et al. 1991), as well as in the PTPases PTPH1 (Yang, et al. 1991), PTP-MEG (Gu, et al. 1991), and PTPD1 (Vogel, et al. 1993). FAP-1 intriguingly contains six GLGF (PDZ/DHR) repeats that are thought to mediate intra-and inter-molecular interactions among protein domains. The third GLGF repeat of FAP-1 was first identified as a domain showing the specific interaction with the C-terminus of Fas receptor (Sato, et al. 1995). This suggests that the GLGF domain may play an important role in targeting proteins to the submembranous cytoskeleton

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and/or in regulating biochemical activity. GLGF repeats have been previously found in guanylate kinases, as well as in the rat post-synaptic density protein (PSD-95) (Cho, et al. 1992), which is a homolog of the *Drosophila* tumor suppressor protein, lethal-(1)-disc-large-1 [*dlg-1*] (Woods, et al 1991; Kitamura, et al. 1994). These repeats may mediate homo- and hetero-dimerization, which could potentially influence PTPase activity, binding to Fas, and/or interactions of FAP-1 with other signal transduction proteins. Recently, it has also been reported that the different PDZ domains of proteins interact with the C-terminus of ion channels and other proteins (Figure 1) (TABLE 1) (Kornau, et al. 1995; Kim, et al. 1995; Matsumine, et al. 1996).

TABLE 1. Proteins that interact with PDZ domains.

Protein	C-terminal sequence	Associated protein	Reference
Fas (APO-1/CD95)	SLV	FAP-1	2
NMDA receptor NR2 subunit	SDV	PSD95	3
Shaker-type K ⁺ channel	TDV	PSD95 & DLG	4
APC	TEV	DLG	5

SUMMARY OF THE INVENTION

This invention provides a composition capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L) (Sequence I.D. No.: 1). Further, the cytoplasmic protein may contain the amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L) (Sequence I.D. No.: 2), wherein X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids and n represents at least 2, but not more than 4. In a preferred embodiment, the amino acid sequence is SLGI (Sequence I.D. No.: 3). Further, the invention provides for a composition when the signal-transducing protein has at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L) (Sequence I.D. No.: 4), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, and the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids.

This invention also provides for a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L). Further this invention provides for a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/L/I) and a cytoplasmic protein.

This invention also provides for a method inhibiting the proliferation of cancer cells, specifically, where the cancer cells are derived from organs comprising the

colon, liver, breast, ovary, testis, lung, stomach, spleen, kidney, prostate, uterus, skin, head, thymus and neck, or the cells are derived from either T-cells or B-cells.

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This invention also provides for a method of treating cancer in a subject in an amount of the composition of effective to result in apoptosis of the cells, specifically, where the cancer cells are derived from
10 organs comprising the thymus, colon, liver, breast, ovary, testis, lung, stomach, spleen, kidney, prostate, uterus, skin, head and neck, or the cells are derived from either T-cells or B-cells.

15 This invention also provides for a method of inhibiting the proliferation of virally infected cells, specifically wherein the virally infected cells are infected with the Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus, Adenovirus, Human T-cell lymphotropic
20 virus, type 1 or HIV.

This invention also provides a pharmaceutical composition comprising compositions capable of inhibiting specific binding between a signal-transducing protein and a
25 cytoplasmic protein.

This invention also provides a pharmaceutical composition comprising compounds identified to be capable of inhibiting specific binding between a signal-transducing
30 protein and a cytoplasmic protein.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1. Diagram of Fas-associated phosphatase-1 protein, showing the six GLGF (PDZ/DHR) domain repeats;
5 comparison of similar membrane binding sites with other proteins and proteins that contain GLGF (PDZ/DHR) repeats.

10 Figures 2A, 2B, 2C and 2D. Mapping of the minimal region of the C-terminal of Fas required for the binding to FAP-1. Numbers at right show each independent clone (Figures 2C and 2D).

2A. Strategy for screening of a random peptide library by the yeast two-hybrid system.

15 2B. Alignment of the C-terminal 15 amino acids of Fas between human (Sequence I.D. No.: 5), rat (Sequence I.D. No.: 6), and mouse (Sequence I.D. No.: 7).

20 2C. The results of screening a semi-random peptide library. Top row indicates the amino acids which were fixed based on the homology between human and rat. Dash lines show unchanged amino acids.

25 2D. The results of screening a random peptide library (Sequence I.D. No.: 8, Sequence I.D. No.: 9, Sequence I.D. No.: 10, Sequence I.D. No.: 11, Sequence I.D. No.: 12, Sequence I.D. No.: 13, Sequence I.D. No.: 14, Sequence I.D. No.: 15, Sequence I.D. No.: 16, Sequence I.D. No.: 17, respectively).

30 Figures 3A, 3B and 3C. Inhibition assay of Fas/FAP-1 binding *in vitro*.

35 3A. Inhibition assay of Fas/FAP-1 binding using the C-terminal 15 amino acids of Fas. GST-Fas fusion protein (191-355) was used for *in vitro* binding assay (lane 1, 3-10). GST-Fas fusion protein (191-320) (lane 2) and 1 mM human PAMP (N-terminal 20 amino acids of proadrenomedullin, M.W. 2460.9)

(lane 3) were used as negative controls. The concentrations of the C-terminal 15 amino acids added were 1 (lane 4), 3 (lane 5), 10 (lane 6), 30 (lane 7), 100 (lane 8), 300 (lane 9), and 1000 μ M (lane 10).

3B. Inhibition assay of Fas/FAP-1 binding using the truncated peptides corresponding to the C-terminal 15 amino acids of Fas. All synthetic peptides were acetylated for this inhibition assay (Sequence I.D. No.: 4, Sequence I.D. No.: 18, Sequence I.D. No.: 19, Sequence I.D. No.: 20, Sequence I.D. No.: 21, Sequence I.D. No.: 22, Sequence I.D. No.: 23, respectively).

3C. Inhibitory effect of Fas/FAP-1 binding using the scanned tripeptides.

Figures 4A, 4B, 4C and 4D.

4A. Interaction of the C-terminal 3 amino acids of Fas with FAP-1 in yeast.

4B. Interaction of the C-terminal 3 amino acids of Fas with FAP-1 in vitro.

4C. Immuno-precipitation of native Fas with GST-FAP-1.

4D. Inhibition of Fas/FAP-1 binding with Ac-SLV or Ac-SLY.

Figures 5A, 5B, 5C, 5D, 5E and 5F. Microinjection of Ac-SLV into the DLD-1 cell line. Triangles identify the cells both that were could be microinjected with Ac-SLV and that showed condensed chromatin identified. On the other hand, only one cell of the area appeared apoptotic when microinjected with Ac-SLY.

5A. Representative examples of the cells microinjected with Ac-SLV in the presence of 500 ng/ml CH11 are shown in phase contrast.

5B. Representative examples of the cells microinjected with AC-SLY in the presence of 500 ng/ml CH11 are shown in phase contrast.

- 5C. Representative examples of the cells microinjected with Ac-SLV in the presence of 500 ng/ml CH11 are shown stained with FITC.
- 5D. Representative examples of the cells microinjected with AC-SLY in the presence of 500 ng/ml CH11 are shown stained with FITC.
- 5E. Representative examples of the cells microinjected with Ac-SLV in the presence of 500 ng/ml CH11 are shown with fluorescent DNA staining with Hoechst 33342.
- 5F. Representative examples of the cells microinjected with AC-SLY in the presence of 500 ng/ml CH11 are shown in fluorescent DNA staining with Hoechst 33342.

Figure 6. Quantitation of apoptosis in microinjected DLD-1 cells.

Figures 7A, 7B, 7C, 7D, 7E, 7F, 7G, and 7H.

- 7A. Amino acid sequence of human nerve growth factor receptor (Sequence I.D. No.: 24).
- 7B. Amino acid sequence of human CD4 receptor (Sequence I.D. No. 25).
- 7C. The interaction of Fas-associated phosphatase-1 to the C-terminal of nerve growth factor receptor (NGFR) (p75).
- 7D. Amino acid sequence of human colorectal mutant cancer protein (Sequence I.D. No.: 26).
- 7E. Amino acid sequence of protein kinase C, alpha type.
- 7F. Amino acid sequence of serotonin 2A receptor (Sequence I.D. No.: 27).
- 7G. Amino acid sequence of serotonin 2B receptor (Sequence I.D. No.: 28).
- 7H. Amino acid sequence of adenomatosis polyposis coli protein (Sequence I.D. No.: 29).

Figure 8. Representation of the structural characteristics of p75 NGFR (low-affinity nerve growth factor receptor).

5 Figure 9. Comparison of the C-terminal ends of Fas and p75 NGFR.

10 Figure 10. In vitro interaction of ³⁵S-labeled FAP-1 with various receptors expressed as GST fusion proteins. The indicated GST fusion proteins immobilized on glutathione-Sepharose beads were incubated with in vitro translated, ³⁵S-labeled FAP-1 protein. After the beads were washed, retained FAP-1 protein was analyzed by SDS-PAGE and autoradiography.

15 Figures 11A and 11B. In vitro interaction ³⁵S-labeled FAP-1 with GST-p75 deletion mutants.

11A. Schematic representation of the GST fusion proteins containing the cytoplasmic domains of p75 and p75 deletion mutants. Binding of FAP-1 to the GST fusion proteins with various p75 deletion mutants is depicted at the right and is based on data from (11B).

20 11B. Interaction of in vitro translated, ³⁵S-labeled FAP-1 protein with various GST fusion proteins immobilized on glutathione-Sepharose beads. After the beads were washed, retained FAP-1 protein was analyzed by SDS-PAGE and autoradiography.

25 30 Figure 12. The association between LexA-C-terminal cytoplasmic region of p75NGFR and VP16-FAP-1. The indicated yeast strains were constructed by transformation and the growth of colonies was tested. +/- indicates the growth of colonies on his⁻ plate.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, amino acid residues are abbreviated as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.

In order to facilitate an understanding of the material which follows, certain frequently occurring methods and/or terms are best described in Sambrook, et al., 1989.

The present invention provides for a composition capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, and each slash within such parentheses separating the alternative amino acids. Further, the cytoplasmic protein may contain the amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L), wherein X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids and n represents at least 2, but not more than 4. Specifically, in a preferred embodiment, the cytoplasmic protein contains the amino acid sequence SLGI.

The amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L) is also well-known in the art as "GLGF (PDZ/DHR) amino acid domain." As used herein, "GLGF (PDZ/DHR) amino acid domain" means the amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L).

In a preferred embodiment, the signal-transducing protein

-11-

has at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, and the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids.

The compositions of the subject invention may be, but not limited to, antibodies, inorganic compounds, organic compounds, peptides, peptidomimetic compounds, polypeptides or proteins, fragments or derivatives which share some or all properties, e.g. fusion proteins. The composition may be naturally occurring and obtained by purification, or may be non-naturally occurring and obtained by synthesis.

Specifically, the composition may be a peptide containing the sequence (S/T)-X-(V/I/L)-COOH, wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids. In preferred embodiments, the peptide contains one of the following sequences: DSENSNFRNEIQSLV, RNEIQSLV, NEIQSLV, EIQSLV, IQSLV, QSLV, SLV, IPPDSEDGNEEQSLV, DSEMYNFRSQLASVV, IDLASEFLFLSNSFL, PPTCSQANSGRISTL, SDSNMNMNELSEV, QNFRTYIVSFV, RETIESTV, RGFISSLV, TIQSVI, ESLV. A further preferred embodiment would be an organic compound which has the sequence Ac-SLV-COOH, wherein the Ac represents an acetyl and each - represents a peptide bond.

An example of the subject invention is provided infra. Acetylated peptides may be automatically synthesized on

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an Advanced ChemTech ACT357 using previously published procedures by analogy. Wang resin was used for each run and N^α-Fmoc protection was used for all amino acids, and then 20% piperidine/DMF and coupling was completed using
5 DIC/HOBt and subsequently HBTU/DIEA. After the last amino acid was coupled, the growing peptide on the resin was acetylated with Ac₂O/DMF. The acetylated peptide was purified by HPLC and characterized by FAB-MS and ¹H-NMR.

10 Further, one skilled in the art would know how to construct derivatives of the above-described synthetic peptides coupled to non-acetyl groups, such as amines.

15 This invention also provides for a composition capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such
20 parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, and a cytoplasmic protein.

25 The compositions of the subject invention includes antibodies, inorganic compounds, organic compounds, peptides, peptidomimetic compounds, polypeptides or proteins, fragments or derivatives which share some or all properties, e.g. fusion proteins.

30 This invention also provides a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L),
35 wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses

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separating the alternative amino acids, which comprises
(a) contacting the cytoplasmic protein bound to the
signal-transducing protein with a plurality of compounds
under conditions permitting binding between a known
5 compound previously shown to be able to displace the
signal-transducing protein bound to the cytoplasmic
protein and the bound cytoplasmic protein to form a
complex; and (b) detecting the displaced signal-
transducing protein or the complex formed in step (a)
10 wherein the displacement indicates that the compound is
capable of inhibiting specific binding between the
signal-transducing protein and the cytoplasmic protein.

The inhibition of the specific binding between the
15 signal-transducing protein and the cytoplasmic protein
may affect the transcription activity of a reporter gene.

Further, in step (b), the displaced cytoplasmic protein
or the complex is detected by comparing the transcription
20 activity of a reporter gene before and after the
contacting with the compound in step (a), where a change
of the activity indicates that the specific binding
between the signal-transducing protein and the
cytoplasmic protein is inhibited and the signal-
transducing protein is displaced.
25

As used herein, the "transcription activity of a reporter
gene" means that the expression level of the reporter
gene will be altered from the level observed when the
30 signal-transducing protein and the cytoplasmic protein
are bound. One can also identify the compound by
detecting other biological functions dependent on the
binding between the signal-transducing protein and the
cytoplasmic protein. Examples of reporter genes are
35 numerous and well-known in the art, including, but not
limited to, histidine resistant genes, ampicillin
resistant genes, β -galactosidase gene.

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Further the cytoplasmic protein may be bound to a solid support. Also the compound may be bound to a solid support and comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

An example of the method is provided infra. One can identify a compound capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein using direct methods of detection such as immuno-precipitation of the cytoplasmic protein and the compound bound to a detectable marker. Further, one could use indirect methods of detection that would detect the increase or decrease in levels of gene expression. As discussed infra, one could construct synthetic peptides fused to a LexA DNA binding domain. These constructs would be transformed into the L40-strain with an appropriate cell line having an appropriate reporter gene. One could then detect whether inhibition had occurred by detecting the levels of expression of the reporter gene. In order to detect the expression levels of the reporter gene, one skilled in the art could employ a variety of well-known methods, e.g. two-hybrid systems in yeast, mammals or other cells.

Further, the contacting of step (a) may be in vitro, in vivo, and specifically in an appropriate cell, e.g. yeast cell or mammalian cell. Examples of mammalian cells include, but not limited to, the mouse fibroblast cell NIH 3T3, CHO cells, HeLa cells, Ltk⁻ cells, Cos cells, etc.

Other suitable cells include, but are not limited to, prokaryotic or eukaryotic cells, e.g. bacterial cells (including gram positive cells), fungal cells, insect cells, and other animals cells.

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Further, the signal-transducing protein may be a cell surface receptor, signal transducer protein, or a tumor suppressor protein. Specifically, the cell surface protein is the Fas receptor and may be expressed in cells derived from organs including, but not limited to, thymus, liver, kidney, colon, ovary, breast, testis, spleen, lung, stomach, prostate, uterus, skin, head, and neck, or expressed in cells comprising T-cells and B-cells. In a preferred embodiment, the T-cells are Jurkat T-cells.

Further, the cell-surface receptor may be a CD4 receptor, p75 receptor, serotonin 2A receptor, or serotonin 2B receptor.

Further, the signal transducer protein may be Protein Kinase-C- α -type.

Further, the tumor suppressor protein may be a adenomatosis polyposis coli tumor suppressor protein or colorectal mutant cancer protein.

Further, the cytoplasmic protein contains the amino acid sequence SLGI, specifically Fas-associated phosphatase-1.

This invention also provides a method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, and a cytoplasmic protein which comprises (a) contacting the signal-transducing protein bound to the cytoplasmic protein with

a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to displace the cytoplasmic protein bound to the signal-transducing protein and bound signal-transducing protein to form a complex; and (b) detecting the displaced cytoplasmic protein or the complex of step (a), wherein the displacement indicates that the compound is capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein. The inhibition of the specific binding between the signal-transducing protein and the cytoplasmic protein affects the transcription activity of a reporter gene. Further, in step (b), the displaced signal-transducing protein or the complex is detected by comparing the transcription activity of a reporter gene before and after the contacting with the compound in step (a), where a change of the activity indicates that the specific binding between the signal-transducing protein and the cytoplasmic protein is inhibited and the cytoplasmic protein is displaced.

Further, in step (b), the displaced cytoplasmic protein or the complex is detected by comparing the transcription activity of a reporter gene before and after the contacting with the compound in step (a), where a change of the activity indicates that the specific binding between the signal-transducing protein and the cytoplasmic protein is inhibited and the signal-transducing protein is displaced.

As used herein, the "transcription activity of a reporter gene" means that the expression level of the reporter gene will be altered from the level observed when the signal-transducing protein and the cytoplasmic protein are bound. One can also identify the compound by detecting other biological functions dependent on the binding between the signal-transducing protein and the

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cytoplasmic protein. Examples of reporter genes are numerous and well-known in the art, including, but not limited to, histidine resistant genes, ampicillin resistant genes, β -galactosidase gene.

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Further, the cytoplasmic protein may be bound to a solid support or the compound may be bound to a solid support, comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

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An example of the method is provided infra. One could identify a compound capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein using direct methods of detection such as immuno-precipitation of the cytoplasmic protein and the compound bound with a detectable marker. Further, one could use indirect methods of detection that would detect the increase or decrease in levels of gene expression. As discussed infra, one could construct synthetic peptides fused to a LexA DNA binding domain. These constructs would be transformed into L40-strain with an appropriate cell line having a reporter gene. One could then detect whether inhibition had occurred by detecting the levels of the reporter gene. Different methods are also well known in the art, such as employing a yeast two-hybrid system to detect the expression of a reporter gene.

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Further the contacting of step (a) can be in vitro or in vivo, specifically in a yeast cell or a mammalian cell. Examples of mammalian cells include, but not limited to, the mouse fibroblast cell NIH 3T3, CHO cells, HeLa cells, Ltk⁻ cells, Cos cells, etc.

30

Other suitable cells include, but are not limited to, prokaryotic or eukaryotic cells, e.g. bacterial cells

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(including gram positive cells), fungal cells, insect cells, and other animals cells.

5 Further, the signal-transducing protein is a cell surface receptor, signal transducer protein, or a tumor suppressor protein. Specifically, the cell surface protein is the Fas receptor and is expressed in cells derived from organs comprising thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, 10 uterus, skin, head and neck, or expressed in cells comprising T-cells and B-cells. In a preferred embodiment, the T-cells are Jurkat T-cells.

15 Further, the cell-surface receptor may be a CD4 receptor, p75 receptor, serotonin 2A receptor, or serotonin 2B receptor.

20 Further, the signal transducer protein may be Protein Kinase-C- α -type.

25 Further, the tumor suppressor protein may be a adenomatosis polyposis coli tumor suppressor protein or colorectal mutant cancer protein.

30 Further, the cytoplasmic protein contains the amino acid sequence SLGI, specifically Fas-associated phosphatase-1.

35 This invention also provides a method of inhibiting the proliferation of cancer cells comprising the above-described composition, specifically, wherein the cancer cells are derived from organs including, but not limited to, thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck, or wherein the cancer cells are derived from cells comprising T-cells and B-cells.

This invention also provides a method of inhibiting the proliferation of cancer cells comprising the compound identified by the above-described method, wherein the cancer cells are derived from organs including, but not limited to, thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck, or wherein the cancer cells are derived from cells comprising T-cells and B-cells.

The invention also provides a method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the above-described composition effective to result in apoptosis of the cells, wherein the cancer cells are derived from organs including, but not limited to, thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck, or wherein the cancer cells are derived from cells comprising T-cells and B-cells.

As used herein "apoptosis" means programmed cell death of the cell. The mechanisms and effects of programmed cell death differs from cell lysis. Some observable effects of apoptosis are: DNA fragmentation and disintegration into small membrane-bound fragments called apoptotic bodies.

Means of detecting whether the composition has been effective to result in apoptosis of the cells are well-known in the art. One means is by assessing the morphological change of chromatin using either phase contrast or fluorescence microscopy.

The invention also provides for a method of inhibiting the proliferation of virally infected cells comprising the above-described composition or the compound identified by the above-described, wherein the virally infected cells comprise Hepatitis B virus, Epstein-Barr

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virus, influenza virus, Papilloma virus, Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

5 The invention also provides a method of treating a virally-infected subject which comprises introducing to the subject's virally- infected cells the above-described composition effective to result in apoptosis of the cells or the compound identified by the above-described method of claim 27 effective to result in apoptosis of the
10 cells, wherein the virally infected cells comprise the Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus, Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

15 Means of detecting whether the composition has been effective to result in apoptosis of the cells are well-known in the art. One means is by assessing the morphological change of chromatin using either phase contrast or fluorescence microscopy.

20 This invention also provides for a pharmaceutical composition comprising the above-described composition of in an effective amount and a pharmaceutically acceptable carrier.

25 This invention also provides for a pharmaceutical composition comprising the compound identified by the above-described method of in an effective amount and a pharmaceutically acceptable carrier.

30 This invention further provides a composition capable of specifically binding a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/L/I), wherein each - represents a peptide bond, each
35 parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, and the X

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represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids. The composition may contain the amino acid sequence (G/S/A/E)-L-G-(F/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, and each slash within such parentheses separating the alternative amino acids. In a preferred embodiment, the composition contains the amino acid sequence (K/R/Q)-X_n-(G/S/A/E)-L-G-(F/I/L). wherein X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids and n represents at least 2, but not more than 4. In another preferred embodiment, the composition contains the amino acid sequence SLGI.

This invention further provides a method for identifying compounds capable of binding to a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/L/I), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, which comprises (a) contacting the signal-transducing protein with a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to bind to the signal-transducing protein to form a complex; and (b) detecting the complex formed in step (a) so as to identify a compound capable of binding to the signal-transducing protein. Specifically, the identified compound contains the amino acid sequence (G/S/A/E)-L-G-(F/I/L). In a further preferred embodiment, the identified compound contains the amino acid sequence SLGI.

Further, in the above-described method, the signal-

transducing protein may be bound to a solid support. Also, the compound may be bound to a solid support, and may comprise an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound,
5 a polypeptide or a protein.

Further, the signal-transducing protein may be a cell-surface receptor or a signal transducer. Specifically, the signal-transducing protein may be the Fas receptor,
10 CD4 receptor, p75 receptor, serotonin 2A receptor, serotonin 2B receptor, or protein kinase-C- α -type.

This invention also provides a method of restoring negative regulation of apoptosis in a cell comprising the
15 above-described composition or a compound identified by the above-described method.

As used herein "restoring negative regulation of apoptosis" means enabling the cell from proceeding onto
20 programmed cell death.

For example, cells that have functional Fas receptors and Fas-associated phosphatase 1 do not proceed onto programmed cell death or apoptosis due to the negative
25 regulation of Fas by the phosphatase. However, if Fas-associated phosphatase 1 is unable to bind to the carboxyl terminus of the Fas receptor ((S/T)-X-(V/L/I) region) , e.g. mutation or deletion of at least one of the amino acids in the amino acid sequence (G/S/A/E)-L-G-
30 (F/I/L), the cell will proceed to apoptosis. By introducing a compound capable of binding to the carboxyl terminus of the Fas receptor, one could mimic the effects of a functional phosphatase and thus restore the negative regulation of apoptosis.

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This invention also provides a method of preventing apoptosis in a cell comprising the above-described

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composition or a compound identified by the above-described method.

5 This invention also provides a means of treating pathogenic conditions caused by apoptosis of relevant cells comprising the above-described composition or the compound identified by the above-described method.

10 This invention is illustrated in the Experimental Details section which follows. These sections are set forth to aid in an understanding of the invention but are not intended to, and should not be construed to, limit in any way the invention as set forth in the claims which follow thereafter.

FIRST SERIES OF EXPERIMENTS

Experimental Details

5 Methods and Materials

1. Screening a semi-random and random peptide library.

To create numerous mutations in a restricted DNA
10 sequence, PCR mutagenesis with degenerate
oligonucleotides was employed according to a protocol
described elsewhere (Hill, et al. 1987). Based on the
homology between human and rat, two palindromic sequences
were designed for construction of semi-random library.
15 The two primers used were
5'-CGGAATTCNNNNNNNNAACAGCNNNNNNNNAATGAANNNCAAAGTCTGNN
NTGAGGATCCTCA-3' (Seq. I.D. No.: 30) and
5'-CGGAATTCGACTCAGAANNNNNNAACTTCAGANNNNNNNATCNNNNNNNNNGT
CTGAGGATCCTCA-3' (Seq. I.D. No.: 31). Briefly, the two
20 primers (each 200 pmol), purified by HPLC, were annealed
at 70 °C for 5 minutes and cooled at 23 °C for 60 minutes.
A Klenow fragment (5 U) was used for filling in with a
dNTP mix (final concentration, 1 mM per each dNTP) at
23°C for 60 minutes. The reaction was stopped with 1 µl
25 of 0.5 M EDTA and the DNA was purified with ethanol
precipitation. The resulting double-stranded DNA was
digested with EcoRI and BamHI and re-purified by
electrophoresis on non-denaturing polyacrylamide gels.
The double-strand oligonucleotides were then ligated into
30 the EcoRI-BamHI sites of the pBTM116 plasmid. The
ligation mixtures were electroporated into the *E. coli*
XL1-Blue MRF' (Stratagene) for the plasmid library. The
large scale transformation was carried out as previously
reported. The plasmid library was transformed into
35 L40-strain cells (*MATa*, *trp1*, *leu2*, *his3*, *ade2*,
LYS2:: (lexAop)⁴-HIS3, *URA3:: (lexAop)⁸-lacZ*) carrying the
plasmid pVP16-31 containing a FAP-1 cDNA (Sato, et al.

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1995). Clones that formed on histidine-deficient medium (His⁺) were transferred to plates containing 40 µg/ml X-gal to test for a blue reaction product (β-gal⁺) in plate and filter assays. The clones selected by His⁺ and β-gal⁺ assay were tested for further analysis. The palindromic oligonucleotide, 5'-CGGAATTC-(NNN)₄₋₁₅-TGAGGATCCTCA-3' (Seq. I.D. No. 32), was used for the construction of the random peptide library.

2. Synthesis of peptides

Peptides were automatically synthesized on an Advanced ChemTech ACT357 by analogy to published procedures (Schnorrenberg and Gerhardt, 1989). Wang resin (0.2-0.3 mmole scale) was used for each run and N^α-Fmoc protection was employed for all amino acids. Deprotection was achieved by treatment with 20% piperidine/DMF and coupling was completed using DIC/HOBt and subsequent HBTU/DIEA. After the last amino acid was coupled, the growing peptide on the resin was acetylated with Ac₂O/DMF. The peptide was cleaved from the resin with concomitant removal of all protecting groups by treating with TFA. The acetylated peptide was purified by HPLC and characterized by FAB-MS and ¹H-NMR.

3. Inhibition assay of Fas/FAP-1 binding using the C-terminal 15 amino acids of Fas.

HFAP-10 cDNA (Sato, et al. 1995) subcloned into the Bluescript vector pSK-II (Stratagene) was in vitro-translated from an internal methionine codon in the presence of ³⁵S-L-methionine using a coupled in vitro transcription/translation system (Promega, TNT lysate) and T7 RNA polymerase. The resulting ³⁵S-labeled protein was incubated with GST-Fas fusion proteins that had been immobilized on GST-Sepharose 4B affinity beads

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(Pharmacia) in a buffer containing 150 mM NaCl, 50 mM Tris [pH 8.0], 5 mM DTT, 2 mM EDTA, 0.1 % NP-40, 1 mM PMSF, 50 μ g/ml leupeptin, 1 mM Benzamidine, and 7 μ g/ml pepstatin for 16 hours at 4 °C. After washing vigorously
5 4 times in the same buffer, associated proteins were recovered with the glutathione-Sepharose beads by centrifugation, eluted into boiling Laemmli buffer, and analyzed by SDS-PAGE and fluorography.

- 10 4. Inhibition assay of terminal 15 amino acids of Fas and inhibitory effect of Fas/FAP-1 binding using diverse tripeptides.

In vitro-translated [³⁵S]HFAP-1 was purified with a NAP-5
15 column (Pharmacia) and incubated with 3 μ M of GST-fusion proteins for 16 hours at 4°C. After washing 4 times in the binding buffer, radioactivity incorporation was determined in a b counter. The percentage of binding inhibition was calculated as follows: percent inhibition
20 = [radioactivity incorporation using GST-Fas (191-335) with peptides - radioactivity incorporation using GST-Fas (191-320) with peptides] / [radioactivity incorporation using GST-Fas (191-335) without peptides - radioactivity incorporation using GST-Fas (191-320) without peptides].
25 n=3.

5. Interaction of the C-terminal 3 amino acids of Fas with FAP-1 in yeast and in vitro.

30 The bait plasmids, pBTM116 (LexA)-SLV, -PLV, -SLY, and -SLA, were constructed and transformed into L40-strain with pVP16-FAP-1 or -ras. Six independent clones from each transformants were picked up for the analysis of growth on histidine-deficient medium. GST-Fas, -SLV, and
35 PLV were purified with GST-Sepharose 4B affinity beads (Pharmacia). The methods for in vitro binding are described above.

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6. Immuno-precipitation of native Fas with GST-FAP-1 and inhibition of Fas/FAP-1 binding with Ac-SLV.

5 GST-fusion proteins with or without FAP-1 were incubated with cell extracts from Jurkat T-cells expressing Fas. The bound Fas was detected by Western analysis using anti-Fas monoclonal antibody (F22120, Transduction Laboratories). The tripeptides, Ac-SLV and Ac-SLY were used for the inhibition assay of Fas/FAP-1 binding.

10 7. Microinjection of Ac-SLV into the DLD-1 cell line. DLD-1 human colon cancer cells were cultured in RPMI 1640 medium containing 10% FCS. For microinjection, cells were plated on CELLocate (Eppendorf) at 1×10^5 cells/2 ml in a 35 mm plastic culture dish and grown for 1 day. Just before microinjection, Fas monoclonal antibodies CH11 (MBL International) was added at the concentration of 500 ng/ml. All microinjection experiments were performed using an automatic microinjection system (Eppendorf transjector 5246, micro-manipulator 5171 and Femtotips) (Pantel, et al. 1995). Synthetic tripeptides were suspended in 0.1% (w/v) FITC-Dextran (Sigma)/K-PBS at the concentration of 100 mM. The samples were microinjected into the cytoplasmic region of DLD-1 cells. Sixteen to 20 hours postinjection, the cells were washed with PBS and stained with 10 μ g/ml Hoechst 33342 in PBS. After incubation at 37°C for 30 minutes, the cells were photographed and the cells showing condensed chromatin were counted as apoptotic.

- 30 8. Quantitation of apoptosis in microinjected DLD-1 cells.

35 For each experiment, 25-100 cells were microinjected. Apoptosis of microinjected cells was determined by assessing morphological changes of chromatin using phase contrast and fluorescence microscopy (Wang, et al., 1995;

McGahon, et al., 1995). The data are means +/- S.D. for two or three independent determinations.

Discussion

5

In order to identify the minimal peptide stretch in the C-terminal region of the Fas receptor necessary for FAP-1 binding, an *in vitro* inhibition assay of Fas/FAP-1 binding was used using a series of synthetic peptides as well as yeast two-hybrid system peptide libraries (Figure 2A). First, semi-random libraries (based on the homology between human and rat Fas) (Figures 2B and 2C) of 15 amino acids fused to a LexA DNA binding domain were constructed and co-transformed into yeast strain L40 with pVP16-31 (Sato, et al. 1995) that was originally isolated as FAP-1. After the selection of 200 His⁺ colonies from an initial screen of 5.0×10^6 (Johnson, et al. 1986) transformants, 100 colonies that were β -galactosidase positive were picked for further analysis. Sequence analysis of the library plasmids encoding the C-terminal 15 amino acids revealed that all of the C-termini were either valine, leucine or isoleucine residues. Second, a random library of 4-15 amino acids fused to a LexA DNA binding domain was constructed and screened according to this strategy (Figure 2D). Surprisingly, all of the third amino acid residues from the C-termini were serine, and the results of C-terminal amino acid analyses were identical to the screening of the semi-random cDNA libraries. No other significant amino acid sequences were found in these library screenings, suggesting that the motifs of the last three amino acids (tS-X-V/L/I) are very important for the association with the third PDZ domain of FAP-1 and play a crucial role in protein-protein interaction as well as for the regulation of Fas-induced apoptosis. To further confirm whether the last three amino acids are necessary and sufficient for Fas/FAP-1 binding, plasmids of the LexA-SLV, -PLV, -PLY,

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-SLY, and -SLA fusion proteins were constructed and co-transformed into yeast with pVP16-FAP-1. The results showed that only LexA-SLV associated with FAP-1, whereas LexA-PLV, -PLY, -SLY, and -SLA did not (Figure 4A). In vitro binding studies using various GST-tripeptide fusions and *in vitro*-translated FAP-1 were consistent with these results (Figure 4B).

In addition to yeast two-hybrid approaches, *in vitro* inhibition assay of Fas/FAP-1 binding was also used. First, a synthetic peptide of the C-terminal 15 amino acids was tested whether it could inhibit the binding of Fas and FAP-1 *in vitro* (Figure 3A). The binding of *in vitro*-translated FAP-1 to GST-Fas was dramatically reduced and dependent on the concentration of the synthetic 15 amino acids of Fas. In contrast with these results, human PAMP peptide (Kitamura, et al. 1994) as a negative control had no effect on Fas/FAP-1 binding activity under the same biochemical conditions. Second, the effect of truncated C-terminal synthetic peptides of Fas on Fas/FAP-1 binding *in vitro* was examined. As shown in Figure 3B, only the three C-terminal amino acids (Ac-SLV) were sufficient to obtain the same level of inhibitory effect on the binding of FAP-1 to Fas as achieved with the 4-15 synthetic peptides. Furthermore, Fas/FAP-1 binding was extensively investigated using the scanned tripeptides to determine the critical amino acids residues required for inhibition (Figure 3C). The results revealed that the third amino acids residues from the C-terminus, and the C-terminal amino acids having the strongest inhibitory effect were either serine or threonine; and either valine, leucine, or isoleucine, respectively. However, there were no differences among the second amino acid residues from the C-terminus with respect to their inhibitory effect on Fas/FAP-1 binding. These results were consistent with those of the yeast two-hybrid system (Figures 2C and 2D). Therefore, it was

concluded that the C-terminal three amino acids (SLV) are critical determinants of Fas binding to the third PDZ domain of FAP-1 protein.

5 To further substantiate that the PDZ domain interacts with tS/T-X-V/L/I under more native conditions, GST-fused FAP-1 proteins were tested for their ability to interact with Fas expressed in Jurkat T-cells. The results revealed that the tripeptide Ac-SLV, but not Ac-SLY, 10 abolished in a dose-dependent manner the binding activity of FAP-1 to Fas proteins extracted from Jurkat T-cells (Figures 4C and 4D). This suggests that the C-terminal amino acids tSLV are the minimum binding site for FAP-1, and that the amino acids serine and valine are critical 15 for this physical association.

To next examine the hypothesis that the physiological association between the C-terminal three amino acids of Fas and the third PDZ domain of FAP-1 is necessary for the *in vivo* function of FAP-1 as a negative regulator of Fas-mediated signal transduction, a microinjection experiment was employed with synthetic tripeptides in a colon cancer cell line, DLD-1, which expresses both Fas and FAP-1, and is resistant to Fas-induced apoptosis. 20 The experiments involved the direct microinjection of the synthetic tripeptides into the cytoplasmic regions of single cells and the monitoring of the physiological response to Fas-induced apoptosis *in vivo*. The results showed that microinjection of Ac-SLV into DLD-1 cells 25 dramatically induced apoptosis in the presence of Fas-monoclonal antibodies (CH11, 500 ng/ml) (Figures 5A, 5E and Figure 6), but that microinjection of Ac-SLY and PBS/K did not (Figures 5B, 5F and Figure 6). These results strongly support the hypothesis that the physical association of FAP-1 with the C-terminus of Fas is 30 essential for protecting cells from Fas-induced apoptosis. 35

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In summary, it was found that the C-terminal SLV of Fas is alone necessary and sufficient for binding to the third PDZ domain of FAP-1. Secondly, it is proposed that the new consensus motif of tS/T-X-V/L/I for such binding to the PDZ domain, instead of tS/T-X-V. It is therefore possible that FAP-1 plays important roles for the modulation of signal transduction pathways in addition to its physical interaction with Fas. Thirdly, it is demonstrated that the targeted induction of Fas-mediated apoptosis in colon cancer cells by direct microinjection of the tripeptide Ac-SLV. Further investigations including the identification of a substrate(s) of FAP-1 and structure-function analysis will provide insight to the potential therapeutic applications of Fas/FAP-1 interaction in cancer as well as provide a better understanding of the inhibitory effect of FAP-1 on Fas-mediated signal transduction.

SECOND SERIES OF EXPERIMENTS

FAP-1 was originally identified as a membrane-associated protein tyrosine phosphatase which binds to the C-terminus of Fas, and possesses six PDZ domains (also known as DHR domain or GLGF repeat). PDZ domain has recently been shown as a novel module for specific protein-protein interaction, and it appears to be important in the assembly of membrane proteins and also in linking signaling molecules in a multiprotein complex. In recent comprehensive studies, it was found that the third PDZ domain of FAP-1 specifically recognized the sequence motif t(S/T)-X-V and interacts with the C-terminal three amino acids SLV of Fas (Fig. 9). In order to investigate the possibility that FAP-1 also interacts with the C-terminal region of p75NGFR (Fig. 8), an in vitro binding assay, was performed as well as, a yeast two-hybrid analysis by using a series of deletion mutants of p75NGFR. The results revealed that the C-terminal cytoplasmic region of p75NGFR, which is highly conserved among all species, interacts with FAP-1 (Fig. 10). Furthermore, the C-terminal three amino acids SPV of p75NGFR were necessary and sufficient for the interaction with the third PDZ domain of FAP-1 (Fig. 11A and 11B). Since FAP-1 expression was found highest in fetal brain, these findings imply that interaction of FAP-1 with p75NGFR plays an important role for signal transduction pathway via p75NGFR in neuronal cells as well as in the formation of the initial signal-transducing complex for p75NGFR.

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SEQUENCE LISTING

(1) GENERAL INFORMATION:

- 5 (i) APPLICANT: Takaaki Sato and Junn Yanagisawa
- 10 (ii) TITLE OF INVENTION: COMPOUNDS THAT INHIBIT THE
INTERACTION BETWEEN SIGNAL-
TRANSDUCING PROTEINS AND THE GLGF
(PDZ/DHR) DOMAIN AND USES THEREOF
- (iii) NUMBER OF SEQUENCES: 33
- 15 (iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Cooper & Dunham LLP
(B) STREET: 1185 Avenue of the Americas
(C) CITY: New York
(D) STATE: New York
20 (E) COUNTRY: U.S.A.
(F) ZIP: 10036
- (v) COMPUTER READABLE FORM:
25 (A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30
- 30 (vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: Not Yet Known
(B) FILING DATE: 18-JUL-1997
(C) CLASSIFICATION:
- 35 (viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: White, John P
(B) REGISTRATION NUMBER: 28,678
(C) REFERENCE/DOCKET NUMBER: 0575/48962-A-PCT/JPW/JKM
- 40 (ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (212) 278-0400
(B) TELEFAX: (212) 391-0525
- (2) INFORMATION FOR SEQ ID NO:1:
- 45 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
50 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (iii) HYPOTHETICAL: NO
- 55 (iv) ANTI-SENSE: NO
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
Gly/Ser/Ala/Glu Leu Gly Phe/Ile/Leu
60 1
- (2) INFORMATION FOR SEQ ID NO:2:
- 65 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid

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(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Lys/Arg/Gln Xaa(n) Gly/Ser/Ala/Glu Leu Gly Phe/Ile/Leu
1 5

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Ser Leu Gly Ile
1

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Ser/Thr Xaa Val/Ile/Leu
1

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

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Asp Ser Glu Asn Ser Asn Phe Arg Asn Glu Ile Gln Ser Leu Val
1 5 10 15

5 (2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
10 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Ser Ile Ser Asn Ser Arg Asn Glu Asn Gly Gln Ser Leu Glu
1 5 10 15

20 (2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
25 (B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

30 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Ser Thr Pro Asp Thr Gly Asn Glu Asn Gly Gln Cys Leu Glu
1 5 10 15

35 (2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
40 (B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

45 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Glu Ser Leu Val
50 1

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
55 (B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

60 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Thr Ile Gln Ser Val Ile
65 1 5

-39-

- (2) INFORMATION FOR SEQ ID NO:10:
- (i) SEQUENCE CHARACTERISTICS:
5 (A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:
- Arg Gly Phe Ile Ser Ser Leu Val
1 5
- 15 (2) INFORMATION FOR SEQ ID NO:11:
- (i) SEQUENCE CHARACTERISTICS:
20 (A) LENGTH: 8 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- 25 (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:
- Arg Glu Thr Ile Glu Ser Thr Val
30 1 5
- (2) INFORMATION FOR SEQ ID NO:12:
- 35 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
40 (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:
- 45 Gln Asn Phe Arg Thr Tyr Ile Val Ser Phe Val
1 5 10
- (2) INFORMATION FOR SEQ ID NO:13:
- 50 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 13 amino acids
(B) TYPE: amino acid
55 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: peptide
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:
- 60 Ser Asp Ser Asn Met Asn Met Asn Glu Leu Ser Glu Val
1 5 10
- 65 (2) INFORMATION FOR SEQ ID NO:14:
- (i) SEQUENCE CHARACTERISTICS:

-40-

(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

5 (ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

10 Pro Pro Thr Cys Ser Gln Ala Asn Ser Gly Arg Ile Ser Thr Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:15:

15 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
20 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

25 Ile Asp Leu Ala Ser Glu Phe Leu Phe Leu Ser Asn Ser Phe Leu
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
35 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

40 Asp Ser Glu Met Tyr Asn Phe Arg Ser Gln Leu Ala Ser Val Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
50 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

55 Ile Pro Pro Asp Ser Glu Asp Gly Asn Glu Glu Gln Ser Leu Val
1 5 10 15

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4 amino acids
65 (B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

5 Gln Ser Leu Val
1

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
15 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

20 Ile Gln Ser Leu Val
1 5

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
30 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

35 Glu Ile Gln Ser Leu Val
1 5

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid
45 (C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

50 Asn Glu Ile Gln Ser Leu Val
1 5

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8 amino acids
60 (B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

65 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

-42-

Arg Asn Glu Ile Gln Ser Leu Val
1 5

5 (2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 15 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Asp Ser Glu Asn Ser Asn Phe Arg Asn Glu Ile Gln Ser Leu Val
1 5 10 15

20 (2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 427 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

Met Gly Ala Gly Ala Thr Gly Arg Ala Met Asp Gly Pro Arg Leu Leu
1 5 10 15
Leu Leu Leu Leu Leu Gly Val Ser Leu Gly Gly Ala Lys Glu Ala Cys
20 25 30
Pro Thr Gly Leu Tyr Thr His Ser Gly Glu Cys Cys Lys Ala Cys Asn
35 40 45
Leu Gly Glu Gly Val Ala Gln Pro Cys Gly Ala Asn Gln Thr Val Cys
50 55 60
Glu Pro Cys Leu Asp Ser Val Thr Phe Ser Asp Val Val Ser Ala Thr
65 70 75 80
Glu Pro Cys Lys Pro Cys Thr Glu Cys Val Gly Leu Gln Ser Met Ser
85 90 95
Ala Pro Cys Val Glu Ala Asp Asp Ala Val Cys Arg Cys Ala Tyr Gly
100 105 110
Tyr Tyr Gln Asp Glu Thr Thr Gly Arg Cys Glu Ala Cys Arg Val Cys
115 120 125
Glu Ala Gly Ser Gly Leu Val Phe Ser Cys Gln Asp Lys Gln Asn Thr
130 135 140
Val Cys Glu Glu Cys Pro Asp Gly Thr Tyr Ser Asp Glu Ala Asn His
145 150 155 160
Val Asp Pro Cys Leu Pro Cys Thr Val Cys Glu Asp Thr Glu Arg Gln
165 170 175
Leu Arg Glu Cys Thr Arg Trp Ala Asp Ala Glu Cys Glu Glu Ile Pro
180 185 190

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	Gly	Arg	Trp	Ile	Thr	Arg	Ser	Thr	Pro	Pro	Glu	Gly	Ser	Asp	Ser	Thr
			195					200					205			
5	Ala	Pro	Ser	Thr	Gln	Glu	Pro	Glu	Ala	Pro	Pro	Glu	Gln	Asp	Leu	Ile
	210						215					220				
	Ala	Ser	Thr	Val	Ala	Gly	Val	Val	Thr	Thr	Val	Met	Gly	Ser	Ser	Gln
	225					230					235					240
10	Pro	Val	Val	Thr	Arg	Gly	Thr	Thr	Asp	Asn	Leu	Ile	Pro	Val	Tyr	Cys
					245					250					255	
	Ser	Ile	Leu	Ala	Ala	Val	Val	Val	Gly	Leu	Val	Ala	Tyr	Ile	Ala	Phe
15				260					265				270			
	Lys	Arg	Trp	Asn	Ser	Cys	Lys	Gln	Asn	Lys	Gly	Gly	Ala	Asn	Ser	Arg
			275					280					285			
20	Pro	Val	Asn	Gln	Thr	Pro	Pro	Pro	Glu	Gly	Glu	Lys	Ile	His	Ser	Asp
	290					295						300				
	Ser	Gly	Ile	Ser	Val	Asp	Ser	Gln	Ser	Leu	His	Asp	Gln	Gln	Pro	His
	305					310					315				320	
25	Thr	Gln	Thr	Ala	Ser	Gly	Gln	Ala	Leu	Lys	Gly	Asp	Gly	Gly	Leu	Tyr
					325					330					335	
	Ser	Ser	Leu	Pro	Pro	Ala	Lys	Arg	Glu	Glu	Val	Glu	Lys	Leu	Leu	Asn
30				340					345					350		
	Gly	Ser	Ala	Gly	Asp	Thr	Trp	Arg	His	Leu	Ala	Gly	Glu	Leu	Gly	Tyr
			355					360					365			
35	Gln	Pro	Glu	His	Ile	Asp	Ser	Phe	Thr	His	Glu	Ala	Cys	Pro	Val	Arg
		370					375					380				
	Ala	Leu	Leu	Ala	Ser	Trp	Ala	Thr	Gln	Asp	Ser	Ala	Thr	Leu	Asp	Ala
	385					390					395					400
40	Leu	Leu	Ala	Ala	Leu	Arg	Arg	Ile	Gln	Arg	Ala	Asp	Leu	Val	Glu	Ser
					405					410					415	
	Leu	Cys	Ser	Glu	Ser	Thr	Ala	Thr	Ser	Pro	Val					
45				420					425							

(2) INFORMATION FOR SEQ ID NO:25:

50	(i) SEQUENCE CHARACTERISTICS:
	(A) LENGTH: 458 amino acids
	(B) TYPE: amino acid
	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear
55	(ii) MOLECULE TYPE: peptide
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:
60	Met Asn Arg Gly Val Pro Phe Arg His Leu Leu Leu Val Leu Gln Leu
	1 5 10 15
	Ala Leu Leu Pro Ala Ala Thr Gln Gly Lys Lys Val Val Leu Gly Lys
	20 25 30
65	Lys Gly Asp Thr Val Glu Leu Thr Cys Thr Ala Ser Gln Lys Lys Ser
	35 40 45

-44-

	Ile	Gln	Phe	His	Trp	Lys	Asn	Ser	Asn	Gln	Ile	Lys	Ile	Leu	Gly	Asn
	50						55					60				
5	Gln	Gly	Ser	Phe	Leu	Thr	Lys	Gly	Pro	Ser	Lys	Leu	Asn	Asp	Arg	Ala
	65					70					75					80
	Asp	Ser	Arg	Arg	Ser	Leu	Trp	Asp	Gln	Gly	Asn	Phe	Pro	Leu	Ile	Ile
					85					90					95	
10	Lys	Asn	Leu	Lys	Ile	Glu	Asp	Ser	Asp	Thr	Tyr	Ile	Cys	Glu	Val	Glu
				100					105					110		
	Asp	Gln	Lys	Glu	Glu	Val	Gln	Leu	Leu	Val	Phe	Gly	Leu	Thr	Ala	Asn
			115					120					125			
15	Ser	Asp	Thr	His	Leu	Leu	Gln	Gly	Gln	Ser	Leu	Thr	Ile	Thr	Leu	Glu
	130						135					140				
	Ser	Pro	Pro	Gly	Ser	Ser	Pro	Ser	Val	Gln	Cys	Arg	Ser	Pro	Arg	Gly
20	145					150					155					160
	Lys	Asn	Ile	Gln	Gly	Gly	Lys	Thr	Leu	Ser	Val	Ser	Gln	Leu	Glu	Leu
				165					170						175	
25	Gln	Asp	Ser	Gly	Thr	Trp	Thr	Cys	Thr	Val	Leu	Gln	Asn	Gln	Lys	Lys
				180					185					190		
	Val	Glu	Phe	Lys	Ile	Asp	Ile	Val	Val	Leu	Ala	Phe	Gln	Lys	Ala	Ser
			195					200					205			
30	Ser	Ile	Val	Tyr	Lys	Lys	Glu	Gly	Glu	Gln	Val	Glu	Phe	Ser	Phe	Pro
	210						215					220				
	Leu	Ala	Phe	Thr	Val	Glu	Lys	Leu	Thr	Gly	Ser	Gly	Glu	Leu	Trp	Trp
35	225					230					235					240
	Gln	Ala	Glu	Arg	Ala	Ser	Ser	Ser	Lys	Ser	Trp	Ile	Thr	Phe	Asp	Leu
				245						250					255	
40	Lys	Asn	Lys	Glu	Val	Ser	Val	Lys	Arg	Val	Thr	Gln	Asp	Pro	Lys	Leu
				260					265					270		
	Gln	Met	Gly	Lys	Lys	Leu	Pro	Leu	His	Leu	Thr	Leu	Pro	Gln	Ala	Leu
			275					280					285			
45	Pro	Gln	Tyr	Ala	Gly	Ser	Gly	Asn	Leu	Thr	Leu	Ala	Leu	Glu	Ala	Lys
	290						295					300				
	Thr	Gly	Lys	Leu	His	Gln	Glu	Asn	Val	Leu	Val	Val	Met	Arg	Ala	Thr
50	305					310					315					320
	Gln	Leu	Gln	Lys	Asn	Leu	Thr	Cys	Glu	Val	Trp	Gly	Pro	Thr	Ser	Pro
				325						330					335	
55	Lys	Leu	Met	Leu	Ser	Leu	Lys	Leu	Glu	Asn	Lys	Glu	Ala	Lys	Val	Ser
				340					345					350		
	Lys	Arg	Glu	Lys	Ala	Val	Trp	Val	Leu	Asn	Pro	Glu	Ala	Gly	Met	Trp
			355					360						365		
60	Gln	Cys	Leu	Leu	Ser	Asp	Ser	Gly	Gln	Val	Leu	Leu	Glu	Ser	Asn	Ile
	370						375					380				
	Lys	Val	Leu	Pro	Thr	Trp	Ser	Thr	Pro	Val	Gln	Pro	Met	Ala	Leu	Ile
65	385					390					395					400
	Val	Leu	Gly	Gly	Val	Ala	Gly	Leu	Leu	Leu	Phe	Ile	Gly	Leu	Gly	Ile

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				405					410					415		
	Phe	Phe	Cys	Val	Arg	Cys	Arg	His	Arg	Arg	Arg	Gln	Ala	Glu	Arg	Met
				420					425					430		
5	Ser	Gln	Ile	Lys	Arg	Leu	Leu	Ser	Glu	Lys	Lys	Glu	Cys	Gln	Cys	Pro
			435					440					445			
10	His	Arg	Phe	Gln	Lys	Thr	Cys	Ser	Pro	Ile						
		450					455									

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 828 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

25	Met	Asn	Ser	Gly	Val	Ala	Met	Lys	Tyr	Gly	Asn	Asp	Ser	Ser	Ala	Glu
	1				5					10					15	
	Leu	Ser	Glu	Leu	His	Ser	Ala	Ala	Leu	Ala	Ser	Leu	Lys	Gly	Asp	Ile
				20					25					30		
30	Val	Glu	Leu	Asn	Lys	Arg	Leu	Gln	Gln	Thr	Glu	Arg	Glu	Asp	Leu	Leu
			35				40						45			
	Glu	Lys	Lys	Leu	Ala	Lys	Ala	Gln	Cys	Glu	Gln	Ser	His	Leu	Met	Arg
35		50				55						60				
	Glu	His	Glu	Asp	Val	Gln	Glu	Arg	Thr	Thr	Leu	Arg	Tyr	Glu	Glu	Arg
	65				70						75				80	
40	Ile	Thr	Glu	Leu	His	Ser	Val	Ile	Ala	Glu	Leu	Asn	Lys	Lys	Ile	Asp
				85						90					95	
	Arg	Leu	Gln	Gly	Thr	Thr	Ile	Arg	Glu	Glu	Asp	Glu	Tyr	Ser	Glu	Leu
			100						105					110		
45	Arg	Ser	Glu	Leu	Ser	Gln	Ser	Gln	His	Glu	Val	Asn	Glu	Asp	Ser	Arg
			115					120					125			
	Ser	Met	Asp	Gln	Asp	Gln	Thr	Ser	Val	Ser	Ile	Pro	Glu	Asn	Gln	Ser
50		130					135					140				
	Thr	Met	Val	Thr	Ala	Asp	Met	Asp	Asn	Cys	Ser	Asp	Ile	Asn	Ser	Glu
	145				150						155				160	
	Leu	Gln	Arg	Val	Leu	Thr	Gly	Leu	Glu	Asn	Val	Val	Cys	Gly	Arg	Lys
55					165					170					175	
	Lys	Ser	Ser	Cys	Ser	Leu	Ser	Val	Ala	Glu	Val	Asp	Arg	His	Ile	Glu
			180						185					190		
60	Gln	Leu	Thr	Thr	Ala	Ser	Glu	His	Cys	Asp	Leu	Ala	Ile	Lys	Thr	Val
			195					200					205			
	Glu	Glu	Ile	Glu	Gly	Val	Leu	Gly	Arg	Asp	Leu	Tyr	Pro	Asn	Leu	Ala
65		210					215					220				
	Glu	Glu	Arg	Ser	Arg	Trp	Glu	Lys	Glu	Leu	Ala	Gly	Leu	Arg	Glu	Glu

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	225		230		235		240									
	Asn	Glu	Ser	Leu	Thr	Ala	Met	Leu	Cys	Ser	Lys	Glu	Glu	Glu	Leu	Asn
				245					250						255	
5	Arg	Thr	Lys	Ala	Thr	Met	Asn	Ala	Ile	Arg	Glu	Glu	Arg	Asp	Arg	Leu
			260						265					270		
10	Arg	Arg	Arg	Val	Arg	Glu	Leu	Gln	Thr	Arg	Leu	Gln	Ser	Val	Gln	Ala
			275					280					285			
	Thr	Gly	Pro	Ser	Ser	Pro	Gly	Arg	Leu	Thr	Ser	Thr	Asn	Arg	Pro	Ile
		290					295					300				
15	Asn	Pro	Ser	Thr	Gly	Glu	Leu	Ser	Thr	Ser	Ser	Ser	Ser	Asn	Asp	Ile
	305				310					315						320
	Pro	Ile	Ala	Lys	Ile	Ala	Glu	Arg	Val	Lys	Leu	Ser	Lys	Thr	Arg	Ser
				325						330					335	
20	Glu	Ser	Ser	Ser	Ser	Asp	Arg	Pro	Val	Leu	Gly	Ser	Glu	Ile	Ser	Ser
				340					345					350		
25	Ile	Gly	Val	Ser	Ser	Ser	Val	Ala	Glu	His	Leu	Ala	His	Ser	Leu	Gln
			355					360					365			
	Asp	Cys	Ser	Asn	Ile	Gln	Glu	Ile	Phe	Gln	Thr	Leu	Tyr	Ser	His	Gly
		370				375						380				
30	Ser	Ala	Ile	Ser	Glu	Ser	Lys	Ile	Arg	Glu	Phe	Glu	Val	Glu	Thr	Glu
	385					390					395					400
	Arg	Leu	Asn	Ser	Arg	Ile	Glu	His	Leu	Lys	Ser	Gln	Asn	Asp	Leu	Leu
				405						410					415	
35	Thr	Ile	Thr	Leu	Glu	Glu	Cys	Lys	Ser	Asn	Ala	Glu	Arg	Met	Ser	Met
			420						425					430		
40	Leu	Val	Gly	Lys	Tyr	Glu	Ser	Asn	Ala	Thr	Ala	Leu	Arg	Leu	Ala	Leu
			435					440					445			
	Gln	Tyr	Ser	Glu	Gln	Cys	Ile	Glu	Ala	Tyr	Glu	Leu	Leu	Leu	Ala	Leu
		450				455					460					
45	Ala	Glu	Ser	Glu	Gln	Ser	Leu	Ile	Leu	Gly	Gln	Phe	Arg	Ala	Ala	Gly
	465					470					475					480
	Val	Gly	Ser	Ser	Pro	Gly	Asp	Gln	Ser	Gly	Asp	Glu	Asn	Ile	Thr	Gln
				485						490					495	
50	Met	Leu	Lys	Arg	Ala	His	Asp	Cys	Arg	Lys	Thr	Ala	Glu	Asn	Ala	Ala
			500						505					510		
55	Lys	Ala	Leu	Leu	Met	Lys	Leu	Asp	Gly	Ser	Cys	Gly	Gly	Ala	Phe	Ala
			515					520					525			
	Val	Ala	Gly	Cys	Ser	Val	Gln	Pro	Trp	Glu	Ser	Leu	Ser	Ser	Asn	Ser
		530					535					540				
60	His	Thr	Ser	Thr	Thr	Ser	Ser	Thr	Ala	Ser	Ser	Cys	Asp	Thr	Glu	Phe
	545					550					555					560
	Thr	Lys	Glu	Asp	Glu	Gln	Arg	Leu	Lys	Asp	Tyr	Ile	Gln	Gln	Leu	Lys
				565						570					575	
65	Asn	Asp	Arg	Ala	Ala	Val	Lys	Leu	Thr	Met	Leu	Glu	Leu	Glu	Ser	Ile
				580					585					590		

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5 His Ile Asp Pro Leu Ser Tyr Asp Val Lys Pro Arg Gly Asp Ser Gln
 595 600 605
 Arg Leu Asp Leu Glu Asn Ala Val Leu Met Gln Glu Leu Met Ala Met
 610 615 620
 Lys Glu Glu Met Ala Glu Leu Lys Ala Gln Leu Tyr Leu Leu Glu Lys
 625 630 635 640
 10 Glu Lys Lys Ala Leu Glu Leu Lys Leu Ser Thr Arg Glu Ala Gln Glu
 645 650 655
 Gln Ala Tyr Leu Val His Ile Glu His Leu Lys Ser Glu Val Glu Glu
 660 665 670
 15 Gln Lys Glu Gln Arg Met Arg Ser Leu Ser Ser Thr Ser Ser Gly Ser
 675 680 685
 Lys Asp Lys Pro Gly Lys Glu Cys Ala Asp Ala Ala Ser Pro Ala Leu
 690 695 700
 Ser Leu Ala Glu Leu Arg Thr Thr Cys Ser Glu Asn Glu Leu Ala Ala
 705 710 715 720
 25 Glu Phe Thr Asn Ala Ile Arg Arg Glu Lys Lys Leu Lys Ala Arg Val
 725 730 735
 Gln Glu Leu Val Ser Ala Leu Glu Arg Leu Thr Lys Ser Ser Glu Ile
 740 745 750
 30 Arg His Gln Gln Ser Ala Glu Phe Val Asn Asp Leu Lys Arg Ala Asn
 755 760 765
 Ser Asn Leu Val Ala Ala Tyr Glu Lys Ala Lys Lys Lys His Gln Asn
 770 775 780
 35 Lys Leu Lys Lys Leu Glu Ser Gln Met Met Ala Met Val Glu Arg His
 785 790 795 800
 40 Glu Thr Gln Val Arg Met Leu Lys Gln Arg Ile Ala Leu Leu Glu Glu
 805 810 815
 Glu Asn Ser Arg Pro His Thr Asn Glu Thr Ser Leu
 820 825
 45

(2) INFORMATION FOR SEQ ID NO:27:

50 (i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 672 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear
 55 (ii) MOLECULE TYPE: peptide
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:
 60 Met Ala Asp Val Phe Pro Gly Asn Asp Ser Thr Ala Ser Gln Asp Val
 1 5 10 15
 Ala Asn Arg Phe Ala Arg Lys Gly Ala Leu Arg Gln Lys Asn Val His
 20 25 30
 65 Glu Val Lys Asp His Lys Phe Ile Ala Arg Phe Phe Lys Gln Pro Thr
 35 40 45

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	Phe	Cys	Ser	His	Cys	Thr	Asp	Phe	Ile	Trp	Gly	Phe	Gly	Lys	Gly	Gly
	50						55					60				
5	Phe	Gln	Cys	Gln	Val	Cys	Cys	Phe	Val	Val	His	Lys	Arg	Cys	His	Glu
	65					70					75					80
	Phe	Val	Thr	Phe	Ser	Cys	Pro	Gly	Ala	Asp	Lys	Gly	Pro	Asp	Thr	Asp
					85					90					95	
10	Asp	Pro	Arg	Ser	Lys	His	Lys	Phe	Lys	Ile	His	Thr	Tyr	Gly	Ser	Pro
				100					105					110		
	Thr	Phe	Cys	Asp	His	Cys	Gly	Ser	Leu	Leu	Tyr	Gly	Leu	Ile	His	Gln
			115					120					125			
15	Gly	Met	Lys	Cys	Asp	Thr	Cys	Asp	Met	Asn	Val	His	Lys	Gln	Cys	Val
		130						135					140			
20	Ile	Asn	Val	Pro	Ser	Leu	Cys	Gly	Met	Asp	His	Thr	Glu	Lys	Arg	Gly
	145					150					155					160
	Arg	Ile	Tyr	Leu	Lys	Ala	Glu	Val	Ala	Asp	Glu	Lys	Leu	His	Val	Thr
					165					170					175	
25	Val	Arg	Asp	Ala	Lys	Asn	Leu	Ile	Pro	Met	Asp	Pro	Asn	Gly	Leu	Ser
				180					185					190		
	Asp	Pro	Tyr	Val	Lys	Leu	Lys	Leu	Ile	Pro	Asp	Pro	Lys	Asn	Glu	Ser
			195					200					205			
30	Lys	Gln	Lys	Thr	Lys	Thr	Ile	Arg	Ser	Thr	Leu	Asn	Pro	Gln	Trp	Asn
		210					215					220				
	Glu	Ser	Phe	Thr	Phe	Lys	Leu	Lys	Pro	Ser	Asp	Lys	Asp	Arg	Arg	Leu
35		225				230					235					240
	Ser	Val	Glu	Ile	Trp	Asp	Trp	Asp	Arg	Thr	Thr	Arg	Asn	Asp	Phe	Met
					245					250					255	
40	Gly	Ser	Leu	Ser	Phe	Gly	Val	Ser	Glu	Leu	Met	Lys	Met	Pro	Ala	Ser
				260					265					270		
	Gly	Trp	Tyr	Lys	Leu	Leu	Asn	Gln	Glu	Glu	Gly	Glu	Tyr	Tyr	Asn	Val
			275					280					285			
45	Pro	Ile	Pro	Glu	Gly	Asp	Glu	Glu	Gly	Asn	Met	Glu	Leu	Arg	Gln	Lys
		290					295					300				
	Phe	Glu	Lys	Ala	Lys	Leu	Gly	Pro	Ala	Gly	Asn	Lys	Val	Ile	Ser	Pro
50		305				310					315					320
	Ser	Glu	Asp	Arg	Lys	Gln	Pro	Ser	Asn	Asn	Leu	Asp	Arg	Val	Lys	Leu
					325					330					335	
55	Thr	Asp	Phe	Asn	Phe	Leu	Met	Val	Leu	Gly	Lys	Gly	Ser	Phe	Gly	Lys
				340					345					350		
	Val	Met	Leu	Ala	Asp	Arg	Lys	Gly	Thr	Glu	Glu	Leu	Tyr	Ala	Ile	Lys
			355					360					365			
60	Ile	Leu	Lys	Lys	Asp	Val	Val	Ile	Gln	Asp	Asp	Asp	Val	Glu	Cys	Thr
		370					375					380				
	Met	Val	Glu	Lys	Arg	Val	Leu	Ala	Leu	Leu	Asp	Lys	Pro	Pro	Phe	Leu
65		385				390					395					400
	Thr	Gln	Leu	His	Ser	Cys	Phe	Gln	Thr	Val	Asp	Arg	Leu	Tyr	Phe	Val

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	405	410	415
5	Met Glu Tyr Val Asn Gly Gly Asp Leu Met Tyr His Ile Gln Gln Val 420 425 430		
	Gly Lys Phe Lys Glu Pro Gln Ala Val Phe Tyr Ala Ala Glu Ile Ser 435 440 445		
10	Ile Gly Leu Phe Phe Leu His Lys Arg Gly Ile Ile Tyr Arg Asp Leu 450 455 460		
	Lys Leu Asp Asn Val Met Leu Asp Ser Glu Gly His Ile Lys Ile Ala 465 470 475 480		
15	Asp Phe Gly Met Cys Lys Glu His Met Met Asp Gly Val Thr Thr Arg 485 490 495		
	Thr Phe Cys Gly Thr Pro Asp Tyr Ile Ala Pro Glu Ile Ile Ala Tyr 500 505 510		
20	Gln Pro Tyr Gly Lys Ser Val Asp Trp Trp Ala Tyr Gly Val Leu Leu 515 520 525		
	Tyr Glu Met Leu Ala Gly Gln Pro Pro Phe Asp Gly Glu Asp Glu Asp 530 535 540		
25	Glu Leu Phe Gln Ser Ile Met Glu His Asn Val Ser Tyr Pro Lys Ser 545 550 555 560		
	Leu Ser Lys Glu Ala Val Ser Ile Cys Lys Gly Leu Met Thr Lys His 565 570 575		
30	Pro Ala Lys Arg Leu Gly Cys Gly Pro Glu Gly Glu Arg Asp Val Arg 580 585 590		
35	Glu His Ala Phe Phe Arg Arg Ile Asp Trp Glu Lys Leu Glu Asn Arg 595 600 605		
	Glu Ile Gln Pro Pro Phe Lys Pro Lys Val Cys Gly Lys Gly Ala Glu 610 615 620		
40	Asn Phe Asp Lys Phe Phe Thr Arg Gly Gln Pro Val Leu Thr Pro Pro 625 630 635 640		
	Asp Gln Leu Val Ile Ala Asn Ile Asp Gln Ser Asp Phe Glu Gly Phe 645 650 655		
45	Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val 660 665 670		
50			

(2) INFORMATION FOR SEQ ID NO:28:

55	(i) SEQUENCE CHARACTERISTICS:
	(A) LENGTH: 471 amino acids
	(B) TYPE: amino acid
	(C) STRANDEDNESS: single
	(D) TOPOLOGY: linear
60	(ii) MOLECULE TYPE: peptide
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:
65	Met Asp Ile Leu Cys Glu Glu Asn Thr Ser Leu Ser Ser Thr Thr Asn 1 5 10 15

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	Ser	Leu	Met	Gln	Leu	Asn	Asp	Asp	Thr	Arg	Leu	Tyr	Ser	Asn	Asp	Phe
				20					25					30		
5	Asn	Ser	Gly	Glu	Ala	Asn	Thr	Ser	Asp	Ala	Phe	Asn	Trp	Thr	Val	Asp
			35					40					45			
	Ser	Glu	Asn	Arg	Thr	Asn	Leu	Ser	Cys	Glu	Gly	Cys	Leu	Ser	Pro	Ser
		50					55					60				
10	Cys	Leu	Ser	Leu	Leu	His	Leu	Gln	Glu	Lys	Asn	Trp	Ser	Ala	Leu	Leu
	65					70					75					80
	Thr	Ala	Val	Val	Ile	Ile	Leu	Thr	Ile	Ala	Gly	Asn	Ile	Leu	Val	Ile
					85					90					95	
15	Met	Ala	Val	Ser	Leu	Glu	Lys	Lys	Leu	Gln	Asn	Ala	Thr	Asn	Tyr	Phe
				100					105					110		
	Leu	Met	Ser	Leu	Ala	Ile	Ala	Asp	Met	Leu	Leu	Gly	Phe	Leu	Val	Met
20			115					120					125			
	Pro	Val	Ser	Met	Leu	Thr	Ile	Leu	Tyr	Gly	Tyr	Arg	Trp	Pro	Leu	Pro
		130					135					140				
25	Ser	Lys	Leu	Cys	Ala	Val	Trp	Ile	Tyr	Leu	Asp	Val	Leu	Phe	Ser	Thr
	145					150					155					160
	Ala	Ser	Ile	Met	His	Leu	Cys	Ala	Ile	Ser	Leu	Asp	Arg	Tyr	Val	Ala
					165					170					175	
30	Ile	Gln	Asn	Pro	Ile	His	His	Ser	Arg	Phe	Asn	Ser	Arg	Thr	Lys	Ala
				180					185					190		
	Phe	Leu	Lys	Ile	Ile	Ala	Val	Trp	Thr	Ile	Ser	Val	Gly	Ile	Ser	Met
35			195					200					205			
	Pro	Ile	Pro	Val	Phe	Gly	Leu	Gln	Asp	Asp	Ser	Lys	Val	Phe	Lys	Glu
		210					215					220				
40	Gly	Ser	Cys	Leu	Leu	Ala	Asp	Asp	Asn	Phe	Val	Leu	Ile	Gly	Ser	Phe
	225					230					235					240
	Val	Ser	Phe	Phe	Ile	Pro	Leu	Thr	Ile	Met	Val	Ile	Thr	Tyr	Phe	Leu
					245					250					255	
45	Thr	Ile	Lys	Ser	Leu	Gln	Lys	Glu	Ala	Thr	Leu	Cys	Val	Ser	Asp	Leu
				260					265					270		
	Gly	Thr	Arg	Ala	Lys	Leu	Ala	Ser	Phe	Ser	Phe	Leu	Pro	Gln	Ser	Ser
50			275					280					285			
	Leu	Ser	Ser	Glu	Lys	Leu	Phe	Gln	Arg	Ser	Ile	His	Arg	Glu	Pro	Gly
		290					295					300				
55	Ser	Tyr	Thr	Gly	Arg	Arg	Thr	Met	Gln	Ser	Ile	Ser	Asn	Glu	Gln	Lys
	305					310					315					320
	Ala	Cys	Lys	Val	Leu	Gly	Ile	Val	Phe	Phe	Leu	Phe	Val	Val	Met	Trp
					325					330					335	
60	Cys	Pro	Phe	Phe	Ile	Thr	Asn	Ile	Met	Ala	Val	Ile	Cys	Lys	Glu	Ser
				340					345					350		
	Cys	Asn	Glu	Asp	Val	Ile	Gly	Ala	Leu	Leu	Asn	Val	Phe	Val	Trp	Ile
65			355					360					365			
	Gly	Tyr	Leu	Ser	Ser	Ala	Val	Asn	Pro	Leu	Val	Tyr	Thr	Leu	Phe	Asn

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370 375 380

Lys Thr Tyr Arg Ser Ala Phe Ser Arg Tyr Ile Gln Cys Gln Tyr Lys
385 390 395 400

5 Glu Asn Lys Lys Pro Leu Gln Leu Ile Leu Val Asn Thr Ile Pro Ala
405 410 415

10 Leu Ala Tyr Lys Ser Ser Gln Leu Gln Met Gly Gln Lys Lys Asn Ser
420 425 430

Lys Gln Asp Ala Lys Thr Thr Asp Asn Asp Cys Ser Met Val Ala Leu
435 440 445

15 Gly Lys Gln His Ser Glu Glu Ala Ser Lys Asp Asn Ser Asp Gly Val
450 455 460

Asn Glu Lys Val Ser Cys Val
465 470

20

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:

25 (A) LENGTH: 481 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

35 Met Ala Leu Ser Tyr Arg Val Ser Glu Leu Gln Ser Thr Ile Pro Glu
1 5 10 15

His Ile Leu Gln Ser Thr Phe Val His Val Ile Ser Ser Asn Trp Ser
20 25 30

40 Gly Leu Gln Thr Glu Ser Ile Pro Glu Glu Met Lys Gln Ile Val Glu
35 40 45

Glu Gln Gly Asn Lys Leu His Trp Ala Ala Leu Leu Ile Leu Met Val
50 55 60

45 Ile Ile Pro Thr Ile Gly Gly Asn Thr Leu Val Ile Leu Ala Val Ser
65 70 75 80

50 Leu Glu Lys Lys Leu Gln Tyr Ala Thr Asn Tyr Phe Leu Met Ser Leu
85 90 95

Ala Val Ala Asp Leu Leu Val Gly Leu Phe Val Met Pro Ile Ala Leu
100 105 110

55 Leu Thr Ile Met Phe Glu Ala Met Trp Pro Leu Pro Leu Val Leu Cys
115 120 125

Pro Ala Trp Leu Phe Leu Asp Val Leu Phe Ser Thr Ala Ser Ile Met
130 135 140

60 His Leu Cys Ala Ile Ser Val Asp Arg Tyr Ile Ala Ile Lys Lys Pro
145 150 155 160

65 Ile Gln Ala Asn Gln Tyr Asn Ser Arg Ala Thr Ala Phe Ile Lys Ile
165 170 175

Thr Val Val Trp Leu Ile Ser Ile Gly Ile Ala Ile Pro Val Pro Ile

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	180	185	190
	Lys Gly Ile Glu Thr Asp Val	Asp Asn Pro Asn Asn	Ile Thr Cys Val
	195	200	205
5	Leu Thr Lys Glu Arg Phe Gly	Asp Phe Met Leu Phe Gly	Ser Leu Ala
	210	215	220
10	Ala Phe Phe Thr Pro Leu Ala	Ile Met Ile Val Thr Tyr Phe	Leu Thr
	225	230	235
	Ile His Ala Leu Gln Lys Lys	Ala Tyr Leu Val Lys Asn Lys	Pro Pro
	245	250	255
15	Gln Arg Leu Thr Trp Leu Thr	Val Ser Thr Val Phe Gln Arg	Asp Glu
	260	265	270
	Thr Pro Cys Ser Ser Pro Glu	Lys Val Ala Met Leu Asp Gly	Ser Arg
	275	280	285
20	Lys Asp Lys Ala Leu Pro Asn	Ser Gly Asp Glu Thr Leu Met	Arg Arg
	290	295	300
25	Thr Ser Thr Ile Gly Lys Lys	Ser Val Gln Thr Ile Ser Asn	Glu Gln
	305	310	315
	Arg Ala Ser Lys Val Leu Gly	Ile Val Phe Phe Leu Phe Leu	Met
	325	330	335
30	Trp Cys Pro Phe Phe Ile Thr	Asn Ile Thr Leu Val Leu Cys	Asp Ser
	340	345	350
	Cys Asn Gln Thr Thr Leu Gln	Met Leu Leu Glu Ile Phe Val	Trp Ile
	355	360	365
35	Gly Tyr Val Ser Ser Gly Val	Asn Pro Leu Val Tyr Thr Leu	Phe Asn
	370	375	380
40	Lys Thr Phe Arg Asp Ala Phe	Gly Arg Tyr Ile Thr Cys Asn	Tyr Arg
	385	390	395
	Ala Thr Lys Ser Val Lys Thr	Leu Arg Lys Arg Ser Ser Lys	Ile Tyr
	405	410	415
45	Phe Arg Asn Pro Met Ala Glu	Asn Ser Lys Phe Phe Lys Lys	His Gly
	420	425	430
	Ile Arg Asn Gly Ile Asn Pro	Ala Met Tyr Gln Ser Pro Met	Arg Leu
	435	440	445
50	Arg Ser Ser Thr Ile Gln Ser	Ser Ser Ile Ile Leu Leu Asp	Thr Leu
	450	455	460
55	Leu Leu Thr Glu Asn Glu Gly	Asp Lys Thr Glu Glu Gln Val	Ser Val
	465	470	475
	Val		

60 (2) INFORMATION FOR SEQ ID NO:30:

- (i) SEQUENCE CHARACTERISTICS:
- (A) LENGTH: 2843 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

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(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

5	Met	Ala	Ala	Ala	Ser	Tyr	Asp	Gln	Leu	Leu	Lys	Gln	Val	Glu	Ala	Leu	1	5	10	15
	Lys	Met	Glu	Asn	Ser	Asn	Leu	Arg	Gln	Glu	Leu	Glu	Asp	Asn	Ser	Asn	20	25	30	
10	His	Leu	Thr	Lys	Leu	Glu	Thr	Glu	Ala	Ser	Asn	Met	Lys	Glu	Val	Leu	35	40	45	
	Lys	Gln	Leu	Gln	Gly	Ser	Ile	Glu	Asp	Glu	Ala	Met	Ala	Ser	Ser	Gly	50	55	60	
15	Gln	Ile	Asp	Leu	Leu	Glu	Arg	Leu	Lys	Glu	Leu	Asn	Leu	Asp	Ser	Ser	65	70	75	80
	Asn	Phe	Pro	Gly	Val	Lys	Leu	Arg	Ser	Lys	Met	Ser	Leu	Arg	Ser	Tyr	85	90	95	
	Gly	Ser	Arg	Glu	Gly	Ser	Val	Ser	Ser	Arg	Ser	Gly	Glu	Cys	Ser	Pro	100	105	110	
25	Val	Pro	Met	Gly	Ser	Phe	Pro	Arg	Arg	Gly	Phe	Val	Asn	Gly	Ser	Arg	115	120	125	
	Glu	Ser	Thr	Gly	Tyr	Leu	Glu	Glu	Leu	Glu	Lys	Glu	Arg	Ser	Leu	Leu	130	135	140	
30	Leu	Ala	Asp	Leu	Asp	Lys	Glu	Glu	Lys	Glu	Lys	Asp	Trp	Tyr	Tyr	Ala	145	150	155	160
	Gln	Leu	Gln	Asn	Leu	Thr	Lys	Arg	Ile	Asp	Ser	Leu	Pro	Leu	Thr	Glu	165	170	175	
35	Asn	Phe	Ser	Leu	Gln	Thr	Asp	Met	Thr	Arg	Arg	Gln	Leu	Glu	Tyr	Glu	180	185	190	
	Ala	Arg	Gln	Ile	Arg	Val	Ala	Met	Glu	Glu	Gln	Leu	Gly	Thr	Cys	Gln	195	200	205	
45	Asp	Met	Glu	Lys	Arg	Ala	Gln	Arg	Arg	Ile	Ala	Arg	Ile	Gln	Gln	Ile	210	215	220	
	Glu	Lys	Asp	Ile	Leu	Arg	Ile	Arg	Gln	Leu	Leu	Gln	Ser	Gln	Ala	Thr	225	230	235	240
50	Glu	Ala	Glu	Arg	Ser	Ser	Gln	Asn	Lys	His	Glu	Thr	Gly	Ser	His	Asp	245	250	255	
	Ala	Glu	Arg	Gln	Asn	Glu	Gly	Gln	Gly	Val	Gly	Glu	Ile	Asn	Met	Ala	260	265	270	
55	Thr	Ser	Gly	Asn	Gly	Gln	Gly	Ser	Thr	Thr	Arg	Met	Asp	His	Glu	Thr	275	280	285	
	Ala	Ser	Val	Leu	Ser	Ser	Ser	Ser	Thr	His	Ser	Ala	Pro	Arg	Arg	Leu	290	295	300	
60	Thr	Ser	His	Leu	Gly	Thr	Lys	Val	Glu	Met	Val	Tyr	Ser	Leu	Leu	Ser	305	310	315	320
	Met	Leu	Gly	Thr	His	Asp	Lys	Asp	Asp	Met	Ser	Arg	Thr	Leu	Leu	Ala	325	330	335	

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	Met	Ser	Ser	Ser	Gln	Asp	Ser	Cys	Ile	Ser	Met	Arg	Gln	Ser	Gly	Cys	
				340					345					350			
5	Leu	Pro	Leu	Leu	Ile	Gln	Leu	Leu	His	Gly	Asn	Asp	Lys	Asp	Ser	Val	
			355				360						365				
	Leu	Leu	Gly	Asn	Ser	Arg	Gly	Ser	Lys	Glu	Ala	Arg	Ala	Arg	Ala	Ser	
		370					375					380					
10	Ala	Ala	Leu	His	Asn	Ile	Ile	His	Ser	Gln	Pro	Asp	Asp	Lys	Arg	Gly	
	385				390						395					400	
	Arg	Arg	Glu	Ile	Arg	Val	Leu	His	Leu	Leu	Glu	Gln	Ile	Arg	Ala	Tyr	
					405					410					415		
15	Cys	Ser	Thr	Cys	Trp	Glu	Trp	Gln	Glu	Ala	His	Glu	Pro	Gly	Met	Asp	
				420					425					430			
20	Gln	Asp	Lys	Asn	Pro	Met	Pro	Ala	Pro	Val	Glu	His	Gln	Ile	Cys	Pro	
			435					440					445				
	Ala	Val	Cys	Val	Leu	Met	Lys	Leu	Ser	Phe	Asp	Glu	Glu	His	Arg	His	
		450					455					460					
25	Ala	Met	Asn	Glu	Leu	Gly	Gly	Leu	Gln	Ala	Ile	Ala	Glu	Leu	Leu	Gln	
	465					470					475					480	
	Val	Asp	Cys	Glu	Met	Tyr	Gly	Leu	Thr	Asn	Asp	His	Tyr	Ser	Ile	Thr	
					485					490					495		
30	Leu	Arg	Arg	Tyr	Ala	Gly	Met	Ala	Leu	Thr	Asn	Leu	Thr	Phe	Gly	Asp	
				500					505					510			
35	Val	Ala	Asn	Lys	Ala	Thr	Leu	Cys	Ser	Met	Lys	Gly	Cys	Met	Arg	Ala	
			515					520					525				
	Leu	Val	Ala	Gln	Leu	Lys	Ser	Glu	Ser	Glu	Asp	Leu	Gln	Gln	Val	Ile	
		530					535					540					
40	Ala	Ser	Val	Leu	Arg	Asn	Leu	Ser	Trp	Arg	Ala	Asp	Val	Asn	Ser	Lys	
	545					550					555					560	
	Lys	Thr	Leu	Arg	Glu	Val	Gly	Ser	Val	Lys	Ala	Leu	Met	Glu	Cys	Ala	
					565					570					575		
45	Leu	Glu	Val	Lys	Lys	Glu	Ser	Thr	Leu	Lys	Ser	Val	Leu	Ser	Ala	Leu	
				580					585					590			
50	Trp	Asn	Leu	Ser	Ala	His	Cys	Thr	Glu	Asn	Lys	Ala	Asp	Ile	Cys	Ala	
			595					600					605				
	Val	Asp	Gly	Ala	Leu	Ala	Phe	Leu	Val	Gly	Thr	Leu	Thr	Tyr	Arg	Ser	
		610					615					620					
55	Gln	Thr	Asn	Thr	Leu	Ala	Ile	Ile	Glu	Ser	Gly	Gly	Gly	Ile	Leu	Arg	
	625					630					635					640	
	Asn	Val	Ser	Ser	Leu	Ile	Ala	Thr	Asn	Glu	Asp	His	Arg	Gln	Ile	Leu	
					645					650					655		
60	Arg	Glu	Asn	Asn	Cys	Leu	Gln	Thr	Leu	Leu	Gln	His	Leu	Lys	Ser	His	
				660					665					670			
65	Ser	Leu	Thr	Ile	Val	Ser	Asn	Ala	Cys	Gly	Thr	Leu	Trp	Asn	Leu	Ser	
			675					680					685				
	Ala	Arg	Asn	Pro	Lys	Asp	Gln	Glu	Ala	Leu	Trp	Asp	Met	Gly	Ala	Val	

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	690	695	700	
	Ser Met Leu Lys Asn Leu Ile His Ser Lys His Lys Met Ile Ala Met			
	705	710	715	720
5	Gly Ser Ala Ala Ala Leu Arg Asn Leu Met Ala Asn Arg Pro Ala Lys			
		725	730	735
	Tyr Lys Asp Ala Asn Ile Met Ser Pro Gly Ser Ser Leu Pro Ser Leu			
10		740	745	750
	His Val Arg Lys Gln Lys Ala Leu Glu Ala Glu Leu Asp Ala Gln His			
		755	760	765
15	Leu Ser Glu Thr Phe Asp Asn Ile Asp Asn Ile Ser Pro Lys Ala Ser			
		770	775	780
	His Arg Ser Lys Gln Arg His Lys Gln Ser Leu Tyr Gly Asp Tyr Val			
		785	790	800
20	Phe Asp Thr Asn Arg His Asp Asp Asn Arg Ser Asp Asn Phe Asn Thr			
		805	810	815
	Gly Asn Met Thr Val Leu Ser Pro Tyr Leu Asn Thr Thr Val Leu Pro			
25		820	825	830
	Ser Ser Ser Ser Ser Arg Gly Ser Leu Asp Ser Ser Arg Ser Glu Lys			
		835	840	845
30	Asp Arg Ser Leu Glu Arg Glu Arg Gly Ile Gly Leu Gly Asn Tyr His			
		850	855	860
	Pro Ala Thr Glu Asn Pro Gly Thr Ser Ser Lys Arg Gly Leu Gln Ile			
		865	870	880
35	Ser Thr Thr Ala Ala Gln Ile Ala Lys Val Met Glu Glu Val Ser Ala			
		885	890	895
	Ile His Thr Ser Gln Glu Asp Arg Ser Ser Gly Ser Thr Thr Glu Leu			
40		900	905	910
	His Cys Val Thr Asp Glu Arg Asn Ala Leu Arg Arg Ser Ser Ala Ala			
		915	920	925
45	His Thr His Ser Asn Thr Tyr Asn Phe Thr Lys Ser Glu Asn Ser Asn			
		930	935	940
	Arg Thr Cys Ser Met Pro Tyr Ala Lys Leu Glu Tyr Lys Arg Ser Ser			
		945	950	955
50	Asn Asp Ser Leu Asn Ser Val Ser Ser Ser Asp Gly Tyr Gly Lys Arg			
		965	970	975
	Gly Gln Met Lys Pro Ser Ile Glu Ser Tyr Ser Glu Asp Asp Glu Ser			
55		980	985	990
	Lys Phe Cys Ser Tyr Gly Gln Tyr Pro Ala Asp Leu Ala His Lys Ile			
		995	1000	1005
60	His Ser Ala Asn His Met Asp Asp Asn Asp Gly Glu Leu Asp Thr Pro			
		1010	1015	1020
	Ile Asn Tyr Ser Leu Lys Tyr Ser Asp Glu Gln Leu Asn Ser Gly Arg			
		1025	1030	1035
65	Gln Ser Pro Ser Gln Asn Glu Arg Trp Ala Arg Pro Lys His Ile Ile			
		1045	1050	1055

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	Glu Asp Glu Ile Lys Gln Ser Glu Gln Arg Gln Ser Arg Asn Gln Ser	1060	1065	1070
5	Thr Thr Tyr Pro Val Tyr Thr Glu Ser Thr Asp Asp Lys His Leu Lys	1075	1080	1085
	Phe Gln Pro His Phe Gly Gln Gln Glu Cys Val Ser Pro Tyr Arg Ser	1090	1095	1100
10	Arg Gly Ala Asn Gly Ser Glu Thr Asn Arg Val Gly Ser Asn His Gly	1105	1110	1115
	Ile Asn Gln Asn Val Ser Gln Ser Leu Cys Gln Glu Asp Asp Tyr Glu	1125	1130	1135
15	Asp Asp Lys Pro Thr Asn Tyr Ser Glu Arg Tyr Ser Glu Glu Glu Gln	1140	1145	1150
	His Glu Glu Glu Glu Arg Pro Thr Asn Tyr Ser Ile Lys Tyr Asn Glu	1155	1160	1165
20	Glu Lys Arg His Val Asp Gln Pro Ile Asp Tyr Ser Ile Leu Lys Ala	1170	1175	1180
25	Thr Asp Ile Pro Ser Ser Gln Lys Gln Ser Phe Ser Phe Ser Lys Ser	1185	1190	1195
	Ser Ser Gly Gln Ser Ser Lys Thr Glu His Met Ser Ser Ser Ser Glu	1205	1210	1215
30	Asn Thr Ser Thr Pro Ser Ser Asn Ala Lys Arg Gln Asn Gln Leu His	1220	1225	1230
	Pro Ser Ser Ala Gln Ser Arg Ser Gly Gln Pro Gln Lys Ala Ala Thr	1235	1240	1245
35	Cys Lys Val Ser Ser Ile Asn Gln Glu Thr Ile Gln Thr Tyr Cys Val	1250	1255	1260
40	Glu Asp Thr Pro Ile Cys Phe Ser Arg Cys Ser Ser Leu Ser Ser Leu	1265	1270	1275
	Ser Ser Ala Glu Asp Glu Ile Gly Cys Asn Gln Thr Thr Gln Glu Ala	1285	1290	1295
45	Asp Ser Ala Asn Thr Leu Gln Ile Ala Glu Ile Lys Glu Lys Ile Gly	1300	1305	1310
50	Thr Arg Ser Ala Glu Asp Pro Val Ser Glu Val Pro Ala Val Ser Gln	1315	1320	1325
	His Pro Arg Thr Lys Ser Ser Arg Leu Gln Gly Ser Ser Leu Ser Ser	1330	1335	1340
55	Glu Ser Ala Arg His Lys Ala Val Glu Phe Ser Ser Gly Ala Lys Ser	1345	1350	1355
	Pro Ser Lys Ser Gly Ala Gln Thr Pro Lys Ser Pro Pro Glu His Tyr	1365	1370	1375
60	Val Gln Glu Thr Pro Leu Met Phe Ser Arg Cys Thr Ser Val Ser Ser	1380	1385	1390
65	Leu Asp Ser Phe Glu Ser Arg Ser Ile Ala Ser Ser Val Gln Ser Glu	1395	1400	1405
	Pro Cys Ser Gly Met Val Ser Gly Ile Ile Ser Pro Ser Asp Leu Pro			

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	1410	1415	1420
5	Asp Ser Pro Gly Gln Thr Met Pro Pro Ser Arg Ser Lys Thr Pro Pro 1425 1430 1435 1440		
	Pro Pro Pro Gln Thr Ala Gln Thr Lys Arg Glu Val Pro Lys Asn Lys 1445 1450 1455		
10	Ala Pro Thr Ala Glu Lys Arg Glu Ser Gly Pro Lys Gln Ala Ala Val 1460 1465 1470		
	Asn Ala Ala Val Gln Arg Val Gln Val Leu Pro Asp Ala Asp Thr Leu 1475 1480 1485		
15	Leu His Phe Ala Thr Glu Ser Thr Pro Asp Gly Phe Ser Cys Ser Ser 1490 1495 1500		
	Ser Leu Ser Ala Leu Ser Leu Asp Glu Pro Phe Ile Gln Lys Asp Val 1505 1510 1515 1520		
20	Glu Leu Arg Ile Met Pro Pro Val Gln Glu Asn Asp Asn Gly Asn Glu 1525 1530 1535		
	Thr Glu Ser Glu Gln Pro Lys Glu Ser Asn Glu Asn Gln Glu Lys Glu 1540 1545 1550		
25	Ala Glu Lys Thr Ile Asp Ser Glu Lys Asp Leu Leu Asp Asp Ser Asp 1555 1560 1565		
	Asp Asp Asp Ile Glu Ile Leu Glu Glu Cys Ile Ile Ser Ala Met Pro 1570 1575 1580		
	Thr Lys Ser Ser Arg Lys Ala Lys Lys Pro Ala Gln Thr Ala Ser Lys 1585 1590 1595 1600		
35	Leu Pro Pro Pro Val Ala Arg Lys Pro Ser Gln Leu Pro Val Tyr Lys 1605 1610 1615		
	Leu Leu Pro Ser Gln Asn Arg Leu Gln Pro Gln Lys His Val Ser Phe 1620 1625 1630		
40	Thr Pro Gly Asp Asp Met Pro Arg Val Tyr Cys Val Glu Gly Thr Pro 1635 1640 1645		
	Ile Asn Phe Ser Thr Ala Thr Ser Leu Ser Asp Leu Thr Ile Glu Ser 1650 1655 1660		
	Pro Pro Asn Glu Leu Ala Ala Gly Glu Gly Val Arg Gly Gly Ala Gln 1665 1670 1675 1680		
50	Ser Gly Glu Phe Glu Lys Arg Asp Thr Ile Pro Thr Glu Gly Arg Ser 1685 1690 1695		
	Thr Asp Glu Ala Gln Gly Gly Lys Thr Ser Ser Val Thr Ile Pro Glu 1700 1705 1710		
	Leu Asp Asp Asn Lys Ala Glu Glu Gly Asp Ile Leu Ala Glu Cys Ile 1715 1720 1725		
60	Asn Ser Ala Met Pro Lys Gly Lys Ser His Lys Pro Phe Arg Val Lys 1730 1735 1740		
	Lys Ile Met Asp Gln Val Gln Gln Ala Ser Ala Ser Ser Ser Ala Pro 1745 1750 1755 1760		
65	Asn Lys Asn Gln Leu Asp Gly Lys Lys Lys Lys Pro Thr Ser Pro Val 1765 1770 1775		

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	Lys	Pro	Ile	Pro	Gln	Asn	Thr	Glu	Tyr	Arg	Thr	Arg	Val	Arg	Lys	Asn	
				1780					1785					1790			
5	Ala	Asp	Ser	Lys	Asn	Asn	Leu	Asn	Ala	Glu	Arg	Val	Phe	Ser	Asp	Asn	
			1795					1800					1805				
	Lys	Asp	Ser	Lys	Lys	Gln	Asn	Leu	Lys	Asn	Asn	Ser	Lys	Asp	Phe	Asn	
		1810					1815					1820					
10	Asp	Lys	Leu	Pro	Asn	Asn	Glu	Asp	Arg	Val	Arg	Gly	Ser	Phe	Ala	Phe	
	1825					1830					1835					1840	
	Asp	Ser	Pro	His	His	Tyr	Thr	Pro	Ile	Glu	Gly	Thr	Pro	Tyr	Cys	Phe	
				1845						1850					1855		
15	Ser	Arg	Asn	Asp	Ser	Leu	Ser	Ser	Leu	Asp	Phe	Asp	Asp	Asp	Asp	Val	
				1860					1865					1870			
20	Asp	Leu	Ser	Arg	Glu	Lys	Ala	Glu	Leu	Arg	Lys	Ala	Lys	Glu	Asn	Lys	
		1875						1880					1885				
	Glu	Ser	Glu	Ala	Lys	Val	Thr	Ser	His	Thr	Glu	Leu	Thr	Ser	Asn	Gln	
		1890					1895					1900					
25	Gln	Ser	Ala	Asn	Lys	Thr	Gln	Ala	Ile	Ala	Lys	Gln	Pro	Ile	Asn	Arg	
	1905					1910					1915					1920	
	Gly	Gln	Pro	Lys	Pro	Ile	Leu	Gln	Lys	Gln	Ser	Thr	Phe	Pro	Gln	Ser	
				1925						1930					1935		
30	Ser	Lys	Asp	Ile	Pro	Asp	Arg	Gly	Ala	Ala	Thr	Asp	Glu	Lys	Leu	Gln	
				1940					1945					1950			
35	Asn	Phe	Ala	Ile	Glu	Asn	Thr	Pro	Val	Cys	Phe	Ser	His	Asn	Ser	Ser	
		1955						1960					1965				
	Leu	Ser	Ser	Leu	Ser	Asp	Ile	Asp	Gln	Glu	Asn	Asn	Asn	Lys	Glu	Asn	
		1970				1975						1980					
40	Glu	Pro	Ile	Lys	Glu	Thr	Glu	Pro	Pro	Asp	Ser	Gln	Gly	Glu	Pro	Ser	
	1985				1990						1995					2000	
	Lys	Pro	Gln	Ala	Ser	Gly	Tyr	Ala	Pro	Lys	Ser	Phe	His	Val	Glu	Asp	
				2005					2010					2015			
45	Thr	Pro	Val	Cys	Phe	Ser	Arg	Asn	Ser	Ser	Leu	Ser	Ser	Leu	Ser	Ile	
			2020					2025						2030			
50	Asp	Ser	Glu	Asp	Asp	Leu	Leu	Gln	Glu	Cys	Ile	Ser	Ser	Ala	Met	Pro	
		2035					2040						2045				
	Lys	Lys	Lys	Lys	Pro	Ser	Arg	Leu	Lys	Gly	Asp	Asn	Glu	Lys	His	Ser	
		2050				2055						2060					
55	Pro	Arg	Asn	Met	Gly	Gly	Ile	Leu	Gly	Glu	Asp	Leu	Thr	Leu	Asp	Leu	
	2065				2070						2075					2080	
	Lys	Asp	Ile	Gln	Arg	Pro	Asp	Ser	Glu	His	Gly	Leu	Ser	Pro	Asp	Ser	
				2085					2090						2095		
60	Glu	Asn	Phe	Asp	Trp	Lys	Ala	Ile	Gln	Glu	Gly	Ala	Asn	Ser	Ile	Val	
		2100						2105					2110				
65	Ser	Ser	Leu	His	Gln	Ala	Ala	Ala	Ala	Ala	Cys	Leu	Ser	Arg	Gln	Ala	
		2115				2120						2125					
	Ser	Ser	Asp	Ser	Asp	Ser	Ile	Leu	Ser	Leu	Lys	Ser	Gly	Ile	Ser	Leu	

	2130	2135	2140
5	Gly Ser Pro Phe His Leu Thr Pro Asp Gln Glu Glu Lys Pro Phe Thr 2145 2150 2155 2160		
	Ser Asn Lys Gly Pro Arg Ile Leu Lys Pro Gly Glu Lys Ser Thr Leu 2165 2170 2175		
10	Glu Thr Lys Lys Ile Glu Ser Glu Ser Lys Gly Ile Lys Gly Gly Lys 2180 2185 2190		
	Lys Val Tyr Lys Ser Leu Ile Thr Gly Lys Val Arg Ser Asn Ser Glu 2195 2200 2205		
15	Ile Ser Gly Gln Met Lys Gln Pro Leu Gln Ala Asn Met Pro Ser Ile 2210 2215 2220		
	Ser Arg Gly Arg Thr Met Ile His Ile Pro Gly Val Arg Asn Ser Ser 2225 2230 2235 2240		
20	Ser Ser Thr Ser Pro Val Ser Lys Lys Gly Pro Pro Leu Lys Thr Pro 2245 2250 2255		
25	Ala Ser Lys Ser Pro Ser Glu Gly Gln Thr Ala Thr Thr Ser Pro Arg 2260 2265 2270		
	Gly Ala Lys Pro Ser Val Lys Ser Glu Leu Ser Pro Val Ala Arg Gln 2275 2280 2285		
30	Thr Ser Gln Ile Gly Gly Ser Ser Lys Ala Pro Ser Arg Ser Gly Ser 2290 2295 2300		
	Arg Asp Ser Thr Pro Ser Arg Pro Ala Gln Gln Pro Leu Ser Arg Pro 2305 2310 2315 2320		
35	Ile Gln Ser Pro Gly Arg Asn Ser Ile Ser Pro Gly Arg Asn Gly Ile 2325 2330 2335		
40	Ser Pro Pro Asn Lys Ile Ser Gln Leu Pro Arg Thr Ser Ser Pro Ser 2340 2345 2350		
	Thr Ala Ser Thr Lys Ser Ser Gly Ser Gly Lys Met Ser Tyr Thr Ser 2355 2360 2365		
45	Pro Gly Arg Gln Met Ser Gln Gln Asn Leu Thr Lys Gln Thr Gly Leu 2370 2375 2380		
	Ser Lys Asn Ala Ser Ser Ile Pro Arg Ser Glu Ser Ala Ser Lys Gly 2385 2390 2395 2400		
50	Leu Asn Gln Met Asn Asn Gly Asn Gly Ala Asn Lys Lys Val Glu Leu 2405 2410 2415		
55	Ser Arg Met Ser Ser Thr Lys Ser Ser Gly Ser Glu Ser Asp Arg Ser 2420 2425 2430		
	Glu Arg Pro Val Leu Val Arg Gln Ser Thr Phe Ile Lys Glu Ala Pro 2435 2440 2445		
60	Ser Pro Thr Leu Arg Arg Lys Leu Glu Glu Ser Ala Ser Phe Glu Ser 2450 2455 2460		
	Leu Ser Pro Ser Ser Arg Pro Ala Ser Pro Thr Arg Ser Gln Ala Gln 2465 2470 2475 2480		
65	Thr Pro Val Leu Ser Pro Ser Leu Pro Asp Met Ser Leu Ser Thr His 2485 2490 2495		

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	Ser Ser Val Gln Ala Gly Gly Trp Arg Lys Leu Pro Pro Asn Leu Ser	2500	2505	2510
5	Pro Thr Ile Glu Tyr Asn Asp Gly Arg Pro Ala Lys Arg His Asp Ile	2515	2520	2525
	Ala Arg Ser His Ser Glu Ser Pro Ser Arg Leu Pro Ile Asn Arg Ser	2530	2535	2540
10	Gly Thr Trp Lys Arg Glu His Ser Lys His Ser Ser Ser Leu Pro Arg	2545	2550	2555
	Val Ser Thr Trp Arg Arg Thr Gly Ser Ser Ser Ser Ile Leu Ser Ala	2565	2570	2575
15	Ser Ser Glu Ser Ser Glu Lys Ala Lys Ser Glu Asp Glu Lys His Val	2580	2585	2590
	Asn Ser Ile Ser Gly Thr Lys Gln Ser Lys Glu Asn Gln Val Ser Ala	2595	2600	2605
20	Lys Gly Thr Trp Arg Lys Ile Lys Glu Asn Glu Phe Ser Pro Thr Asn	2610	2615	2620
	Ser Thr Ser Gln Thr Val Ser Ser Gly Ala Thr Asn Gly Ala Glu Ser	2625	2630	2635
25	Lys Thr Leu Ile Tyr Gln Met Ala Pro Ala Val Ser Lys Thr Glu Asp	2645	2650	2655
	Val Trp Val Arg Ile Glu Asp Cys Pro Ile Asn Asn Pro Arg Ser Gly	2660	2665	2670
30	Arg Ser Pro Thr Gly Asn Thr Pro Pro Val Ile Asp Ser Val Ser Glu	2675	2680	2685
	Lys Ala Asn Pro Asn Ile Lys Asp Ser Lys Asp Asn Gln Ala Lys Gln	2690	2695	2700
35	Asn Val Gly Asn Gly Ser Val Pro Met Arg Thr Val Gly Leu Glu Asn	2705	2710	2715
	Arg Leu Asn Ser Phe Ile Gln Val Asp Ala Pro Asp Gln Lys Gly Thr	2725	2730	2735
40	Glu Ile Lys Pro Gly Gln Asn Asn Pro Val Pro Val Ser Glu Thr Asn	2740	2745	2750
	Glu Ser Ser Ile Val Glu Arg Thr Pro Phe Ser Ser Ser Ser Ser Ser	2755	2760	2765
45	Lys His Ser Ser Pro Ser Gly Thr Val Ala Ala Arg Val Thr Pro Phe	2770	2775	2780
	Asn Tyr Asn Pro Ser Pro Arg Lys Ser Ser Ala Asp Ser Thr Ser Ala	2785	2790	2795
50	Arg Pro Ser Gln Ile Pro Thr Pro Val Asn Asn Asn Thr Lys Lys Arg	2805	2810	2815
	Asp Ser Lys Thr Asp Ser Thr Glu Ser Ser Gly Thr Gln Ser Pro Lys	2820	2825	2830
55	Arg His Ser Gly Ser Tyr Leu Val Thr Ser Val	2835	2840	
60				
65				

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(2) INFORMATION FOR SEQ ID NO:31:

5 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 65 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

10 (ii) MOLECULE TYPE: other nucleic acid
(iii) HYPOTHETICAL: NO
(iv) ANTI-SENSE: NO

15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:
CGGAATTCNN NNNNNNNAAC AGCNNNNNNN NNAATGAANN NCAAGTCTG NNNTGAGGAT 60
CCTCA 65

(2) INFORMATION FOR SEQ ID NO:32:

25 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 65 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

30 (ii) MOLECULE TYPE: other nucleic acid
(iv) ANTI-SENSE: NO

35 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:
CGGAATTCGA CTCAGAANNN NNNAACTCA GANNNNNNAT CNNNNNNNNN GTCTGAGGAT 60
CCTCA 65

(2) INFORMATION FOR SEQ ID NO:33:

45 (i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 65 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

50 (ii) MOLECULE TYPE: other nucleic acid
(iv) ANTI-SENSE: NO

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:
55 CGGAATTCNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNNNNNNNN NNNTGAGGAT 60
CCTCA 65

What is claimed is:

1. A composition capable of inhibiting specific binding
between a signal-transducing protein and a
cytoplasmic protein containing the amino acid
sequence (G/S/A/E)-L-G-(F/I/L), wherein each -
represents a peptide bond, each parenthesis encloses
amino acids which are alternatives to one other, and
each slash within such parentheses separating the
alternative amino acids.
2. The composition of claim 1, wherein the cytoplasmic
protein contains the amino acid sequence (K/R/Q)-X_n-
(G/S/A/E)-L-G-(F/I/L), wherein X represents any
amino acid which is selected from the group
comprising the twenty naturally occurring amino
acids and n represents at least 2, but not more than
4.
3. The composition of claim 1, wherein the cytoplasmic
protein contains the amino acid sequence SLGI.
4. The composition of claim 1, wherein the signal-
transducing protein has at its carboxyl terminus the
amino acid sequence (S/T)-X-(V/I/L), wherein each -
represents a peptide bond, each parenthesis encloses
amino acids which are alternatives to one other,
each slash within such parentheses separating the
alternative amino acids, and the X represents any
amino acid which is selected from the group
comprising the twenty naturally occurring amino
acids.
5. The composition of claim 1, wherein the composition
comprises an antibody, an inorganic compound, an
organic compound, a peptide, a peptidomimetic

compound, a polypeptide, or a protein.

- 5 6. The composition of claim 5, wherein the peptide comprises the sequence (S/T)-X-(V/I/L)-COOH, wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids.
- 10 7. The composition of claim 6, wherein the peptide has the amino acid sequence DSENSNFRNEIQSLV.
- 15 8. The composition of claim 6, wherein the peptide has the amino acid sequence RNEIQSLV.
- 20 9. The composition of claim 6, wherein the peptide has the amino acid sequence NEIQSLV.
- 25 10. The composition of claim 6, wherein the peptide has the amino acid sequence EIQLV.
11. The composition of claim 6, wherein the peptide has the amino acid sequence IOSLV.
- 30 12. The composition of claim 6, wherein the peptide has the amino acid sequence QSLV.
13. The composition of claim 6, wherein the peptide has the amino acid sequence SLV.
- 35 14. The composition of claim 6, wherein the peptide has the amino acid sequence IPPDSEDGNEEQSLV.
15. The composition of claim 6, wherein the peptide has

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the amino acid sequence DSEMYNFRSQLASVV.

- 5
16. The composition of claim 6, wherein the peptide has the amino acid sequence IDLASEFLFLSNSFL.
17. The composition of claim 6, wherein the peptide has the amino acid sequence PPTCSQANSGRISTL.
- 10
18. The composition of claim 6, wherein the peptide has the amino acid sequence SDSNMNMNELSEV.
19. The composition of claim 6, wherein the peptide has the amino acid sequence QNFRTYIVSFV.
- 15
20. The composition of claim 6, wherein the peptide has the amino acid sequence RETIESTV.
21. The composition of claim 6, wherein the peptide has the amino acid sequence RGFISSLV.
- 20
22. The composition of claim 6, wherein the peptide has the amino acid sequence TIQSVI.
23. The composition of claim 6, wherein the peptide has the amino acid sequence ESLV.
- 25
24. The composition of claim 6, wherein the organic compound has the sequence Ac-SLV-COOH, wherein the Ac represents an acetyl, each - represent a peptide bond.
- 30
25. A composition capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such
- 35

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parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, and a cytoplasmic protein.

5
26. The composition of claim 25, wherein the composition comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

10
27. A method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein and a cytoplasmic protein containing the amino acid sequence (G/S/A/E)-L-G-(F/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, which comprises:

15
20
(a) contacting the cytoplasmic protein bound to the signal-transducing protein with a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to displace the signal-transducing protein bound to the cytoplasmic protein and the bound cytoplasmic protein to form a complex; and

25
30
(b) detecting the displaced signal-transducing protein or the complex formed in step (a), wherein the displacement indicates that the compound is capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein.

35
28. The method of claim 27, wherein the inhibition of specific binding between the signal-transducing

protein and the cytoplasmic protein affects the transcription activity of a reporter gene.

- 5 29. The method of claim 28, where in step (b) the displaced signal-transducing protein or the complex is detected by comparing the transcription activity of a reporter gene before and after the contacting with the compound in step (a), where a change of the activity indicates that the specific binding between the signal-transducing protein and the cytoplasmic protein is inhibited and the signal-transducing protein is displaced.
- 10 30. The method of claim 27, wherein the cytoplasmic protein is bound to a solid support.
- 15 31. The method of claim 27, wherein the compound is bound to a solid support.
- 20 32. The method of claim 27, wherein the compound comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.
- 25 33. The method of claim 27, wherein the contacting of step (a) is in vitro.
- 30 34. The method of claim 27, wherein the contacting of step (a) is in vivo.
- 35 35. The method of claim 34, wherein the contacting of step (a) is in a yeast cell.
36. The method of claim 34, wherein the contacting or step (a) is in a mammalian cell.
37. The method of claim 27, wherein the signal-

-67-

transducing protein is a cell surface receptor.

38. The method of claim 27, wherein the signal-transducing protein is a signal transducer protein.

39. The method of claim 27, wherein the signal-transducing protein is a tumor suppressor protein.

40. The method of claim 37, wherein the cell surface protein is the Fas receptor.

41. The method of claim 40, wherein the Fas receptor is expressed in cells derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

42. The method of claim 40, wherein the Fas receptor is expressed in cells comprising T-cells and B-cells.

43. The method of claim 37, wherein the cell-surface receptor is the CD4 receptor.

44. The method of claim 37, wherein the cell-surface receptor is the p75 receptor.

45. The method of claim 37, wherein the cell-surface receptor is the serotonin 2A receptor.

46. The method of claim 37, wherein the cell-surface receptor is the serotonin 2B receptor.

47. The method of claim 38, wherein the signal transducer protein is Protein Kinase-C- α -type.

48. The method of claim 39, wherein the tumor suppressor protein is adenomatosis polyposis coli tumor

suppressor protein.

49. The method of claim 39, wherein the tumor suppressor protein is the colorectal mutant cancer protein.
50. The method of claim 27, wherein the cytoplasmic protein contains the amino acid sequence SLGI, wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, and each slash within such parentheses separating the alternative amino acids.
51. The method of claim 40, wherein the cytoplasmic protein is Fas-associated phosphatase-1.
52. A method of identifying a compound capable of inhibiting specific binding between a signal-transducing protein having at its carboxyl terminus the amino acid sequence (S/T)-X-(V/I/L), wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, each slash within such parentheses separating the alternative amino acids, the X represents any amino acid which is selected from the group comprising the twenty naturally occurring amino acids, and a cytoplasmic protein, which comprises:
- (a) contacting the signal-transducing protein bound to the cytoplasmic protein with a plurality of compounds under conditions permitting binding between a known compound previously shown to be able to displace the cytoplasmic protein bound to the signal-transducing protein and the bound signal-transducing protein to form a complex; and

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(b) detecting the displaced cytoplasmic protein or the complex of step (a) wherein the displacement indicates that the compound is capable of inhibiting specific binding between the signal-transducing protein and the cytoplasmic protein.

53. The method of claim 52, wherein the inhibition of specific binding between the signal-transducing protein and the cytoplasmic protein affects the transcription activity of a reporter gene.

54. The method of claim 53, where in step (b) the displaced cytoplasmic protein or the complex is detected by comparing the transcription activity of a reporter gene before and after the contacting with the compound in step (a), where a change of the activity indicates that the specific binding between the signal-transducing protein and the cytoplasmic protein is inhibited and the cytoplasmic protein is displaced.

55. The method of claim 52, wherein the cytoplasmic protein is bound to a solid support.

56. The method of claim 52, wherein the compound is bound to a solid support.

57. The method of claim 52, wherein the compound comprises an antibody, an inorganic compound, an organic compound, a peptide, a peptidomimetic compound, a polypeptide or a protein.

58. The method of claim 52, wherein the contacting of step (a) is in vitro.

59. The method of claim 52, wherein the contacting of

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step (a) is in vivo.

60. The method of claim 59, wherein the contacting of step (a) is in a yeast cell.

61. The method of claim 59, wherein the contacting or step (a) is in a mammalian cell.

62. The method of claim 52, wherein the signal-transducing protein is a cell surface receptor.

63. The method of claim 52, wherein the signal-transducing protein is a signal transducer protein.

64. The method of claim 52, wherein the signal-transducing protein is a tumor suppressor protein.

65. The method of claim 62, wherein the cell surface protein is the Fas receptor.

66. The method of claim 65, wherein the Fas receptor is expressed in cells derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

67. The method of claim 65, wherein the Fas receptor is expressed in cells comprising T-cells and B-cells.

68. The method of claim 62, wherein the cell-surface receptor is the CD4 receptor.

69. The method of claim 62, wherein the cell-surface receptor is the p75 receptor.

70. The method of claim 62, wherein the cell-surface receptor is the serotonin 2A receptor.

71. The method of claim 62, wherein the cell-surface receptor is the serotonin 2B receptor.

5 72. The method of claim 63, wherein the signal transducer protein is Protein Kinase-C- α -type.

73. The method of claim 64, wherein the tumor suppressor protein is adenomatosis polyposis coli tumor suppressor protein.
10

74. The method of claim 64, wherein the tumor suppressor protein is the colorectal mutant cancer protein.

15 75. The method of claim 52, wherein the cytoplasmic protein contains the amino acid sequence SLGI, wherein each - represents a peptide bond, each parenthesis encloses amino acids which are alternatives to one other, and each slash within such parentheses separating the alternative amino acids.
20

76. The method of claim 52, wherein the cytoplasmic protein is Fas-associated phosphatase-1.
25

77. A method inhibiting the proliferation of cancer cells comprising the composition of claim 1.

78. The method of claim 77, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.
30

79. The method of claim 77, wherein the cancer cells are derived from cells comprising T-cells and B-cells.
35

80. A method of inhibiting the proliferation of cancer

-72-

cells comprising the composition of claim 25.

5 81. The method of claim 80, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

10 82. The method of claim 80, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

83. A method of inhibiting the proliferation of cancer cells comprising the compound identified by the method of claim 27.

15 84. The method of claim 83, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

20 85. The method of claim 83, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

25 86. A method of inhibiting the proliferation of cancer cells comprising the compound identified by the method of claim 52.

30 87. The method of claim 86, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

88. The method of claim 86, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

35 89. A method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the composition of claim 1

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effective to result in apoptosis of the cells.

5 90. The method of claim 89, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

10 91. The method of claim 89, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

15 92. A method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the composition of claim 25 effective to result in apoptosis of the cells.

20 93. The method of claim 92, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

25 94. The method of claim 92, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

30 95. A method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the compound identified by the method of claim 27 effective to allow apoptosis of the cells.

35 96. The method of claim 95, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

97. The method of claim 95, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

5 98. A method of treating cancer in a subject which comprises introducing to the subject's cancerous cells an amount of the compound identified by the method of claim 52 effective to result in apoptosis of the cells.

10 99. The method of claim 98, wherein the cancer cells are derived from organs comprising the thymus, liver, kidney, colon, ovary, breast, testis, spleen, stomach, prostate, uterus, skin, head and neck.

100. The method of claim 98, wherein the cancer cells are derived from cells comprising T-cells and B-cells.

15 101. A method of inhibiting the proliferation of virally infected cells comprising the composition of claim 1.

20 102. A method of inhibiting the proliferation of virally infected cells comprising the composition of claim 25.

25 103. A method of inhibiting the proliferation of virally infected cells comprising the compound identified by the method of claim 27.

30 104. A method of inhibiting the proliferation of virally infected cells comprising the compound identified by the method of claim 52.

35 105. The method of claim 101, wherein the virally infected cells comprise Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

106. The method of claim 102, wherein the virally

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infected cells comprise Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

5

107. The method of claim 103, wherein the virally infected cells comprise Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

10

108. The method of claim 104, wherein the virally infected cells comprise Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

15

109. A method of treating a virally-infected subject which comprises introducing to the subject's virally- infected cells the composition of claim 1 effective to result in apoptosis of the cells.

20

110. A method of treating a virally-infected subject which comprises introducing to the subject's virally infected cells the composition of claim 25 effective to result in apoptosis of the cells.

25

111. A method of treating a virally-infected subject which comprises introducing to the subject's virally-infected cells an amount of the compound identified by the method of claim 27 effective to result in apoptosis of the cells.

30

112. A method of treating a virally-infected subject which comprises introducing to the subject's virally- infected cells an amount of the compound identified by the method of claim 52 effective to

35

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result in apoptosis of the cells.

113. The method of claim 109, wherein the virally infected cells comprise the Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

114. The method of claim 110, wherein the virally infected cells comprise the Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

115. The method of claim 111, wherein the virally infected cells comprise the Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

116. The method of claim 112, wherein the virally infected cells comprise the Hepatitis B virus, Epstein-Barr virus, influenza virus, Papilloma virus. Adeno virus, Human T-cell lymphotropic virus, type 1 or HIV.

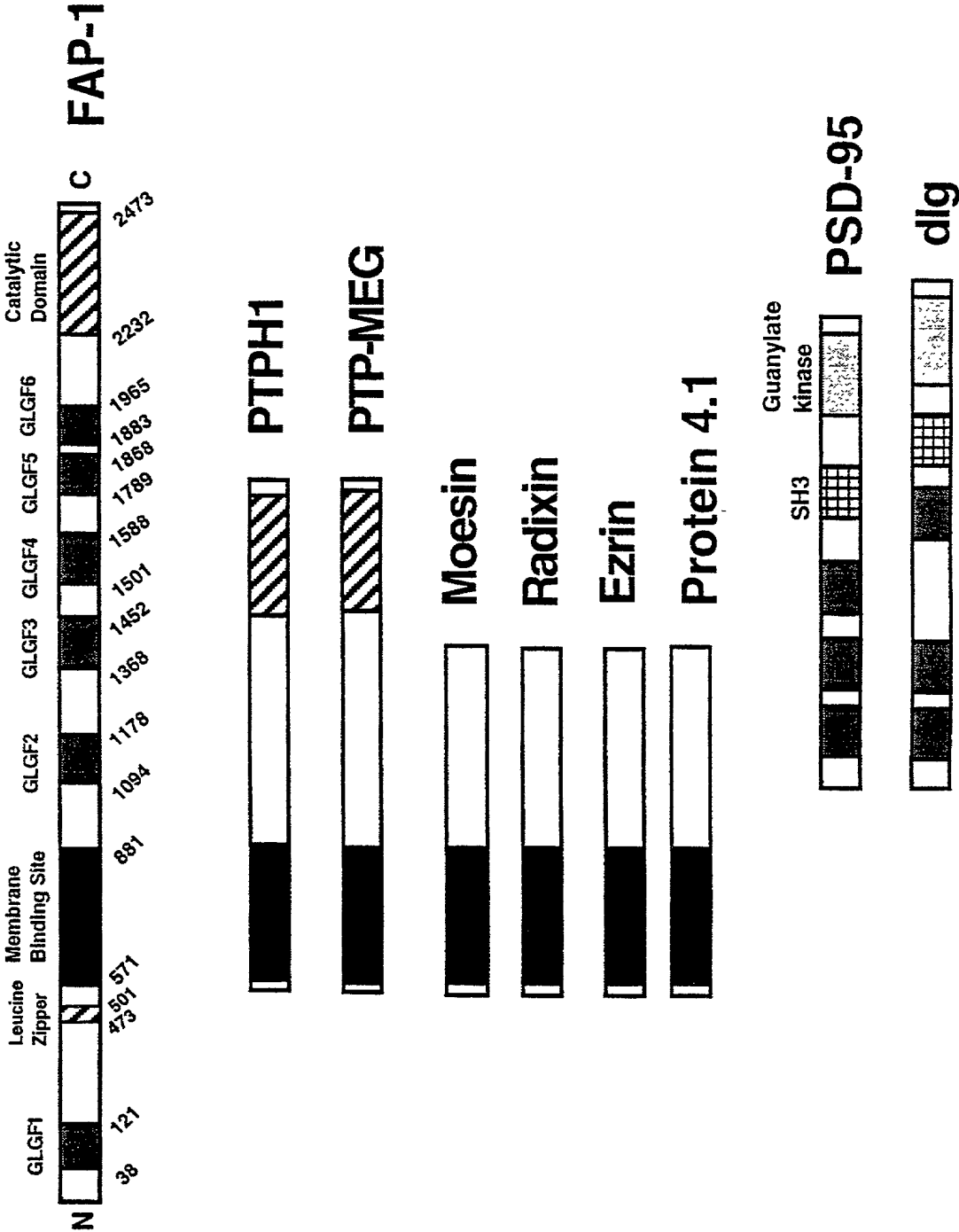
117. A pharmaceutical composition comprising the composition of claim 1 in an effective amount and a pharmaceutically acceptable carrier.

118. A pharmaceutical composition comprising the composition of claim 25 in an effective amount and a pharmaceutically acceptable carrier.

119. A pharmaceutical composition comprising the compound identified by the method of claim 27 in an effective amount and a pharmaceutically acceptable carrier.

120. A pharmaceutical composition comprising the compound identified by the method of claim 52 in an effective amount and a pharmaceutically acceptable carrier.

FIG. 1



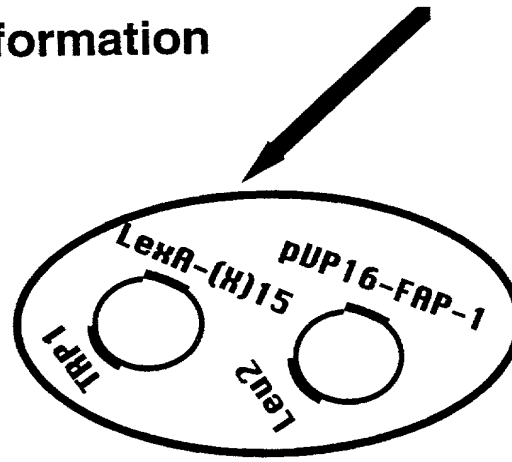
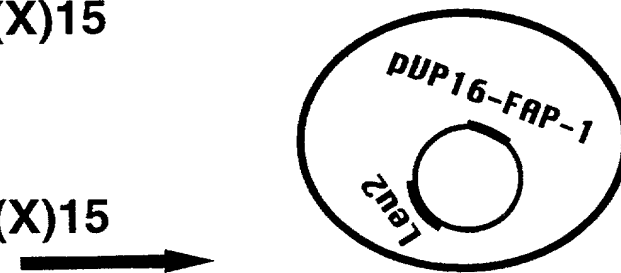
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FIG. 2A

Construction of
pBTM116 (LexA)-(X)15

Library DNAs of
pBTM116 (LexA)-(X)15

Large scale transformation
of yeast L40



His⁺, β -gal⁺

Curing of pVP16-FAP-1

Isolation of
pBTM116 (LexA)-(X)15

Analysis of
DNA sequences

FIG. 2B
Human

D	S	E	N	S	N	F	R	N	E	I	Q	S	L	V
S	I	S	N	S	R	N	E	N	E	G	Q	S	L	E
S	T	P	D	T	G	N	E	N	E	G	Q	C	L	E

FIG. 2C

- - - N S - - - N E - Q S L -

C	Y	A		A	I	G		L					V	12-0
E	N	A		G	V	S		E					V	5-0
W	W	G		A	T	Q		P					V	13-0
E	H	A		Q	Q		Q						V	20-0
N	S	S		F	H	S		L					V	6-2
G	L	R		L	P	P		D					V	9-5
G	S	D		S	G	V		N					V	18-1
D	K	K		R	P	V		N					V	22-1
T	G	K		D	V	W		A					V	71-1
A	S	R		N	E	E		L					I	14-5

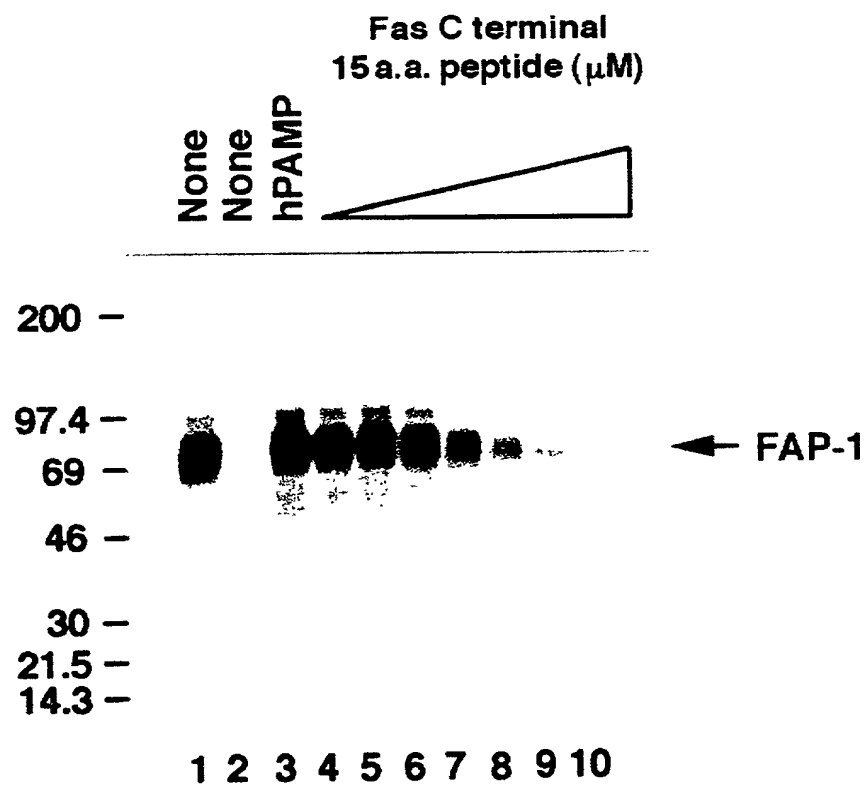
FIG. 2D

I	P	P	D	S	E	D	G	N	E	E	Q	S	L	V	8-1
D	S	E	M	Y	N	F	R	S	Q	L	A	S	V	V	9-3
I	D	L	A	S	E	F	L	F	L	S	N	S	F	L	14-1
P	P	T	C	S	Q	A	N	S	G	R	I	S	T	L	0-2
S	D	S	N	M	N	M	N	E	L	S	E	V			57-5
Q	N	F	R	T	Y	I	V	S	F	V					72-1
R	E	T	I	E	S	T	V								25-9
R	G	F	I	S	S	L	V								16-13
T	I	Q	S	V	I										6-3
E	S	L	V												18-1

Consensus: *t*S-X-V/L/I

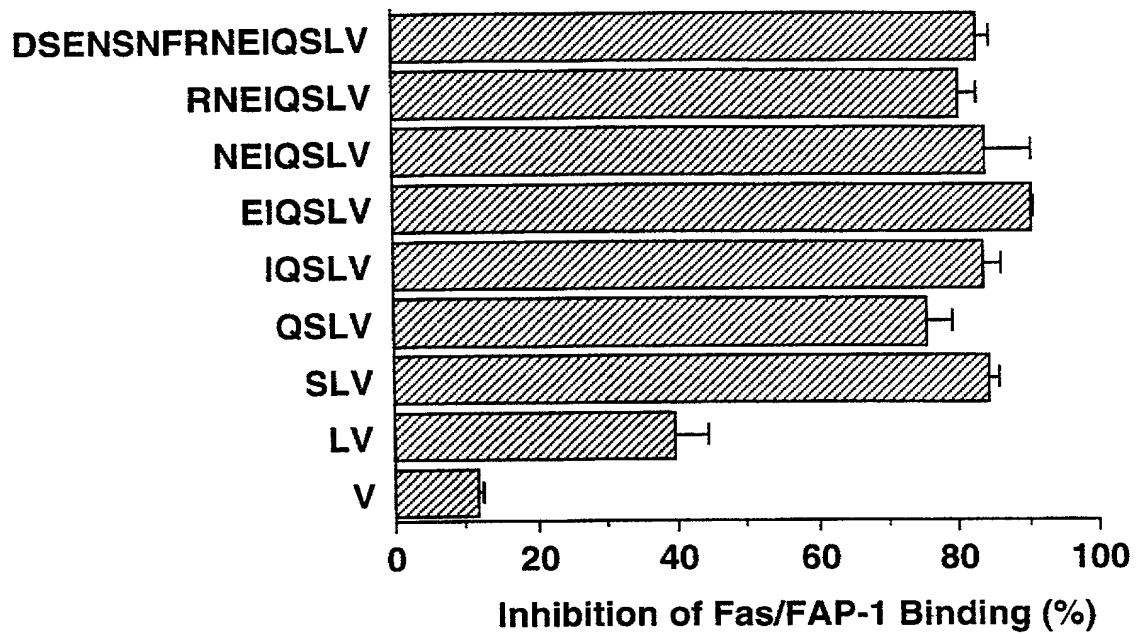
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FIG. 3A



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FIG. 3B



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FIG. 3C

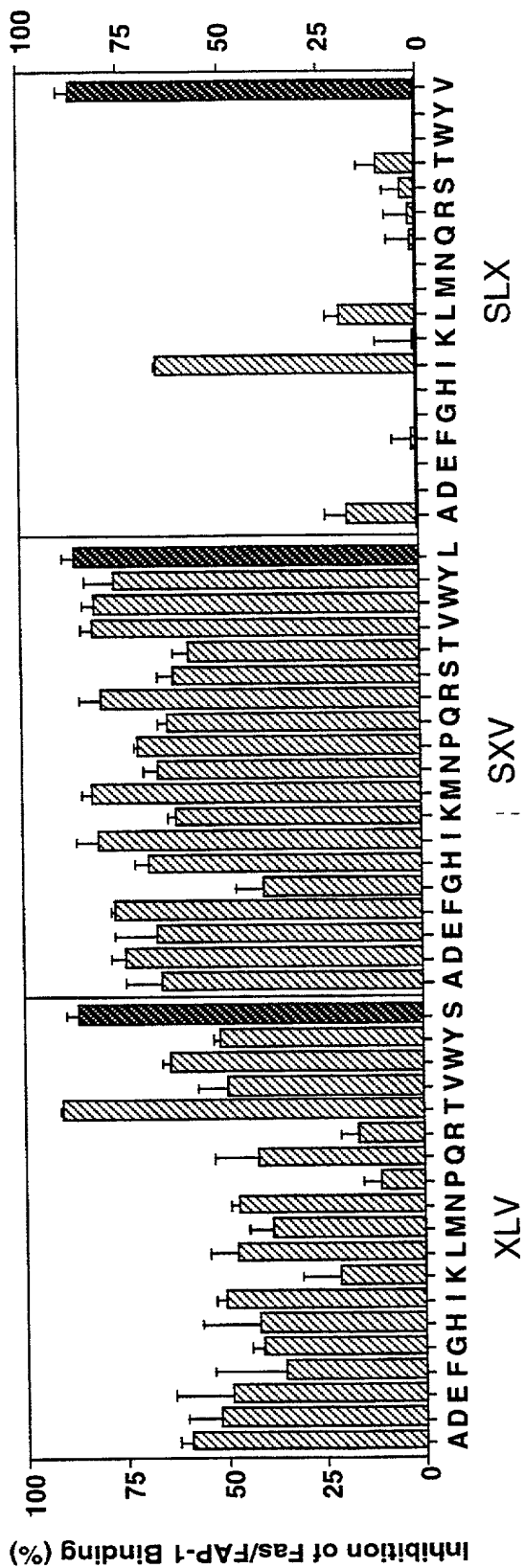
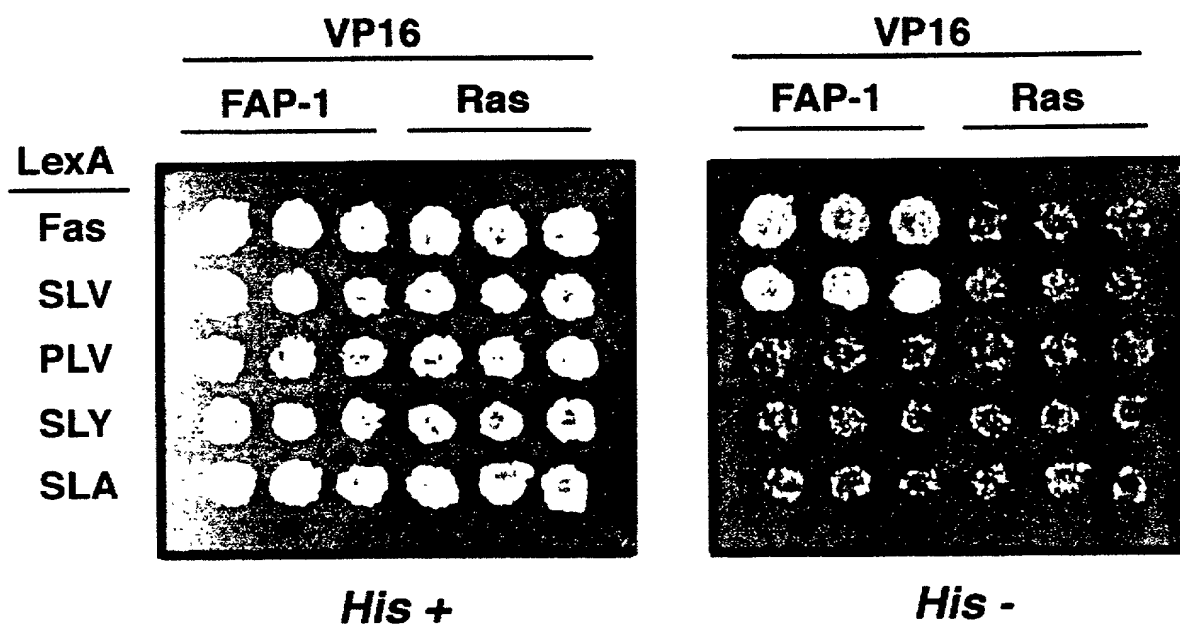
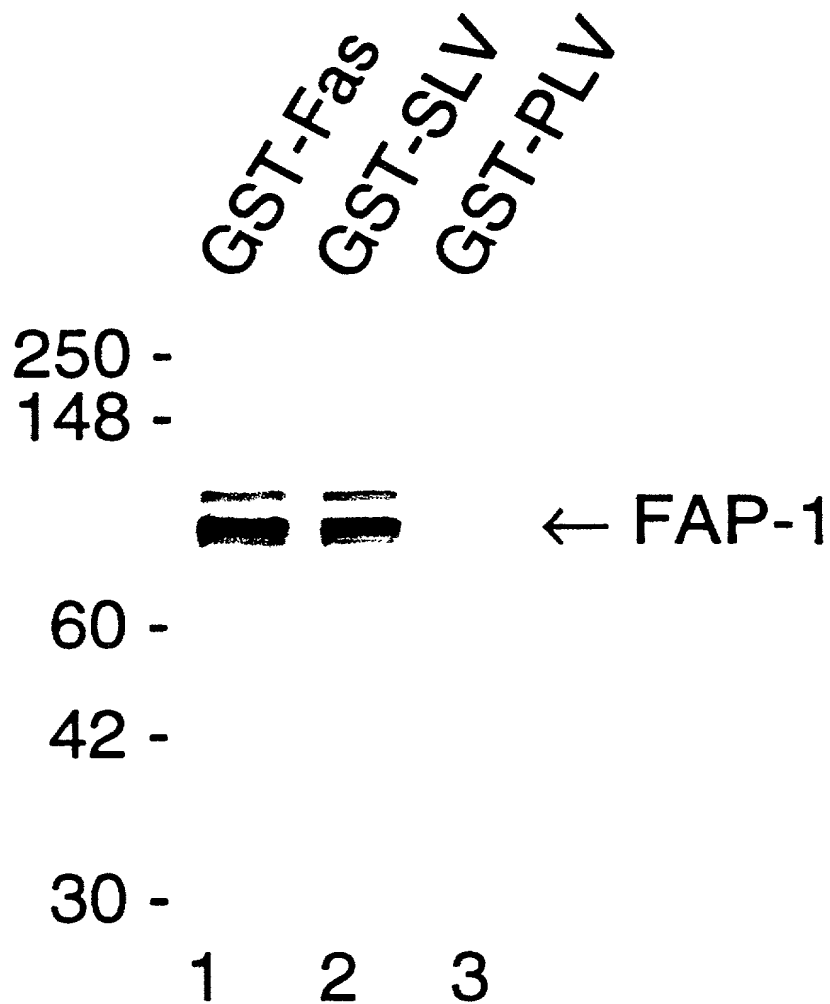


FIG. 4A

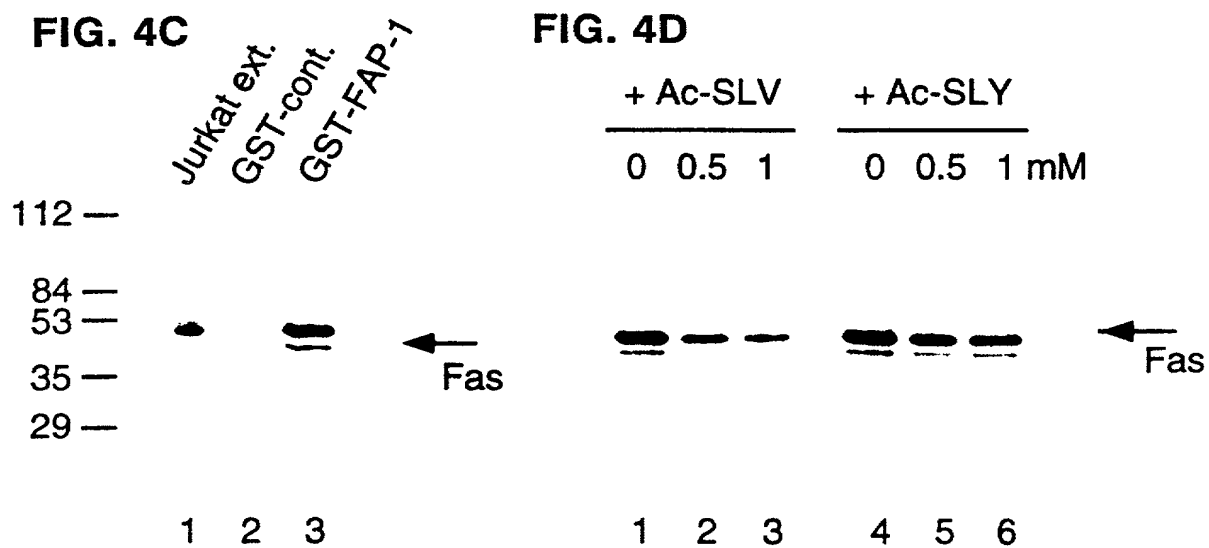


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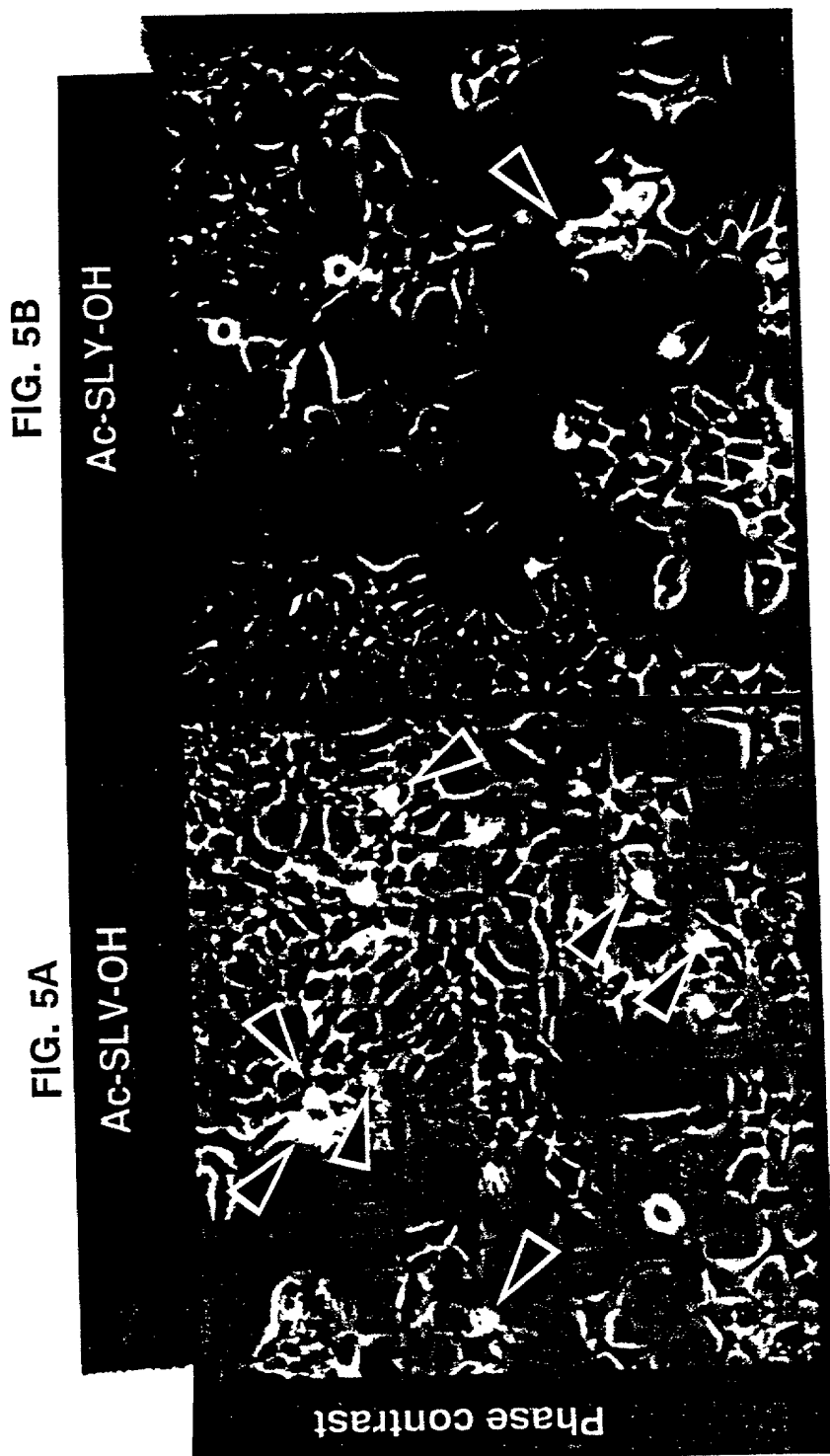
FIG. 4B



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FIG. 5D
Ac-SLY-OH

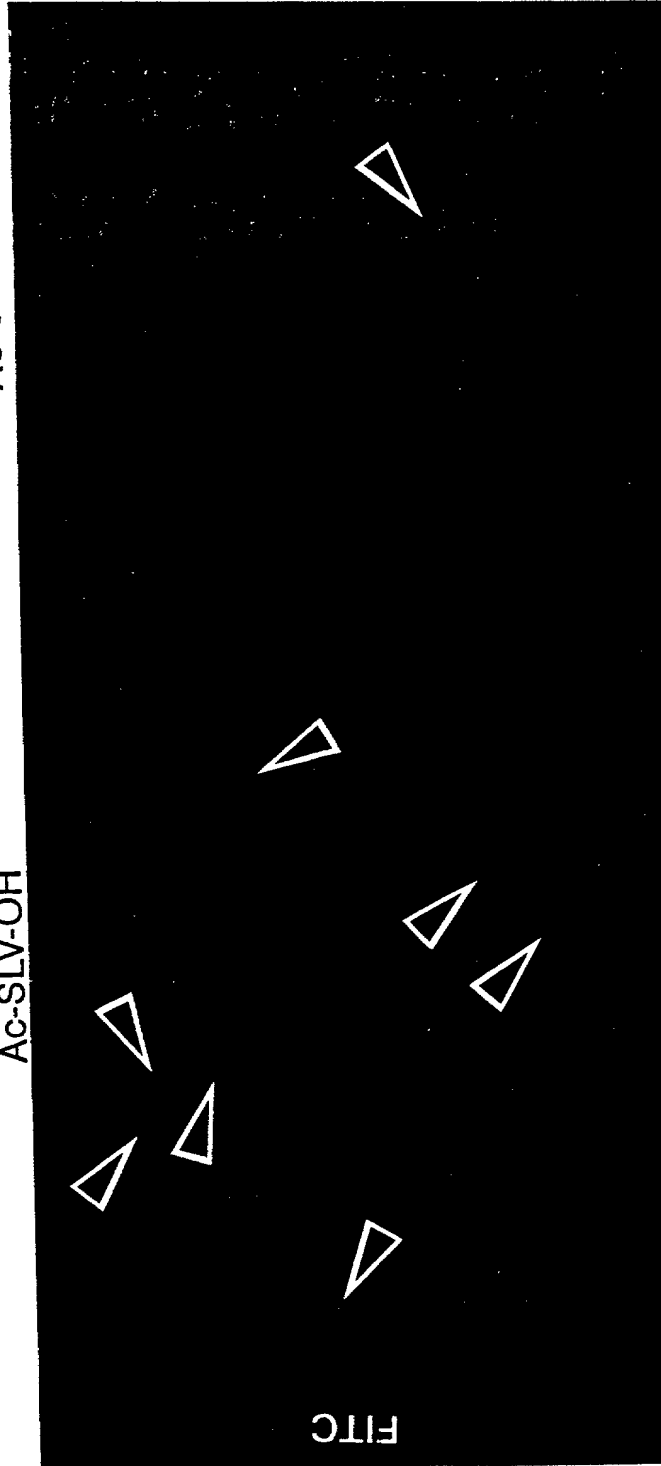
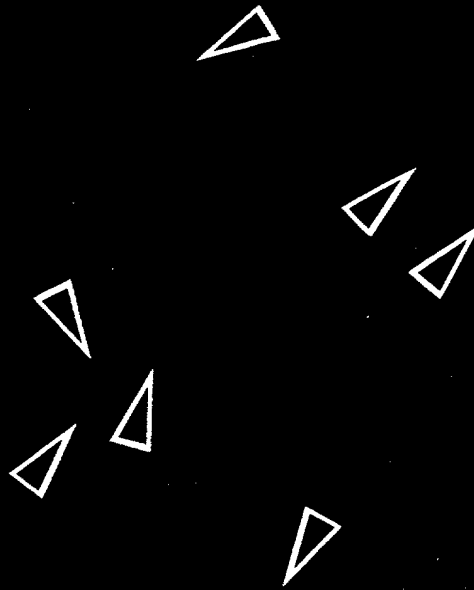


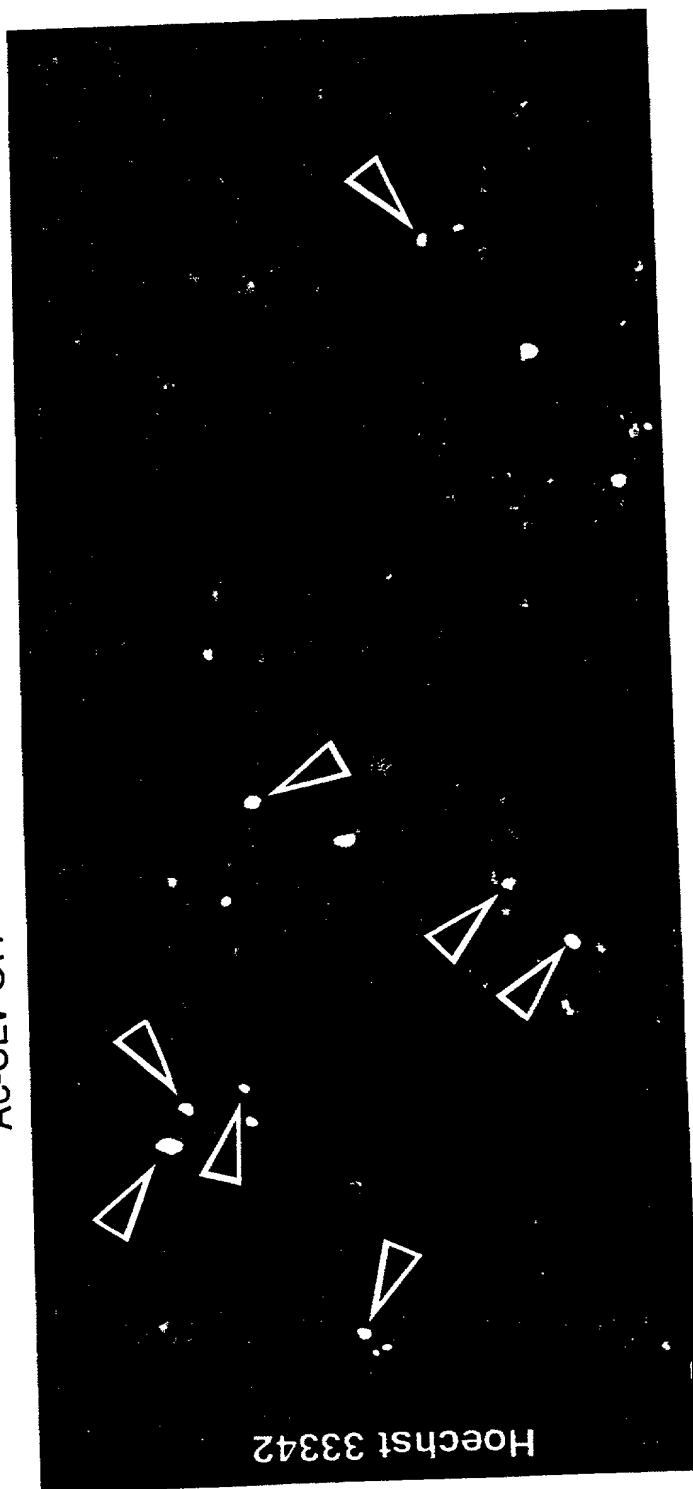
FIG. 5C
Ac-SLV-OH



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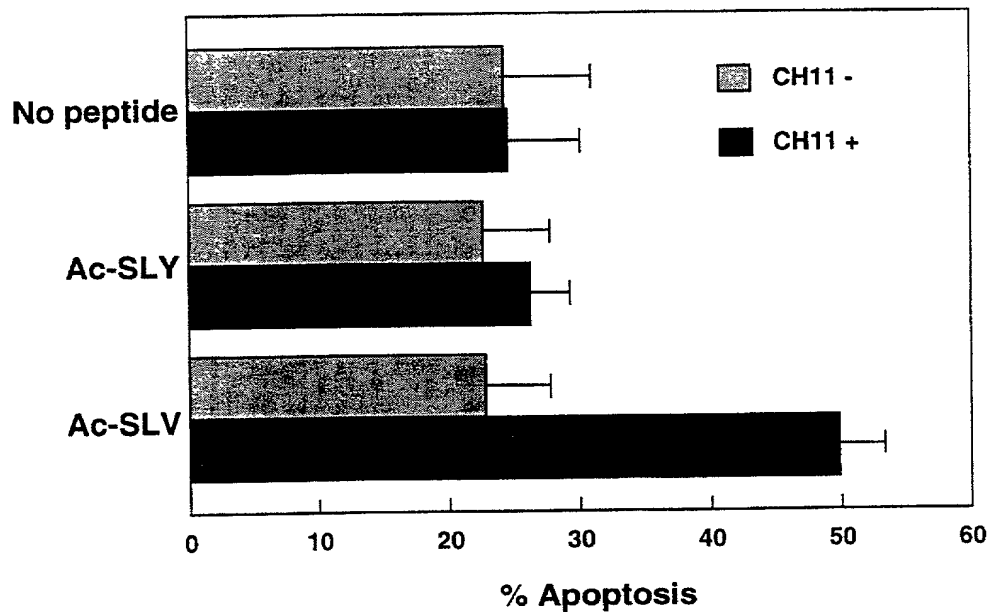
FIG. 5F
Ac-SLY-OH

FIG. 5E
Ac-SLV-OH



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FIG. 6



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FIG. 7A

NGF Receptor

1 mgagatgram dgprlllllll lgvsllggake acptglyths gecckacnlg egvaqpcgan
 61 qtvcepclds vtfsdvvsat epckpctecv glqmsapcv eaddavcrca ygyyqdettg
 121 rceacrvicea gsglvfscqd kqntvceecp dgtysdeanh vdpclpctvc edterqlrec
 181 trwadaecee ipgrwitrst ppegdstap stqeapeppe qdliastvag vttvmgssq
 241 pvvtrgttdn lipvycsila avvglvayi afkrwnsckq nkggansrpv nqtppegek
 301 lhdsgisvd sqslhdqgph tqtasqqalk gdgglysslp pakreevekl lngsagdtwr
 361 hlageelgyqp ehidsfthea cpvrallasw atqdsatlada llaalrrigr adlveslcse
 421 statspv

FIG. 7B

CD4 Receptor

1 mnrgvpfrhl llvlqlallp aatqgkkvvl gkkgdtvelt ctasqkksiq fhwknsnqik
 61 ilgnqgsflt kgpsklndra dsrrslwdqg nfpliiknlk iedsdyice vedqkeevql
 121 lvfgltansd thllqgqslt ltlesppgss psvqcrsprg kniqggktils vsqlelqdsq
 181 twtctvlqnq kkvefkidiv vlafqkassi vykkegeqve fsfplafte kltgsgelww
 241 qaerasssks witfdlknke vsvkrvtqdp klqmgkklpl hltpqalp qagsnltla
 301 leaktgklhq evnlvmrat qlqknltece wghtspklml slklenkeak vskrekavvw
 361 lnpeagmwqc llsdsgqvlv esnikvlptw stpvqpmlali vlggvaglll figlgifcvc
 421 rcrhrrrqae rmsqikrlls ekktcgcphr fqktcspi

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FIG. 7C

Species	C-terminal sequences of NGFR (p75)	Binding activity of FAP-1
Human	tSESTATSPV-COOH	+
Rat	tSESTATSPV-COOH	+
Chicken	tSESTATSPV-COOH	+

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FIG. 7D

1 mnsqvamkyg ndsaaelsel hsaalaslkq divolnkrilq qtererdlle kklakaqceq
 61 ehlmhredv qerttlryee ritelhsvia elnkkidrlq gttireedey selrselsqs
 121 qhevnedrsz mdqdtstsvsi penqetmvtat dmdncsdins elqrvltgle nvvcgrkkss
 181 csisvaevdr hieqlttase hcdlaiktve eiegvlgddl ypnlaeersr wekelaglire
 241 enesltamlc skeelnrnk atmnairer drlrrrvrel qtrlqsvqat gppsppgrits
 301 tnrplnptg elstssssnd ipiakiaerv klsktrssss sdrpvlgsse issigvsssv
 361 aehlahslqd csniqelfgt lyshgsaise skirefeyet erlnsriehi ksqndlltit
 421 leeksnaer mslvgkyes natalrlalq yseqcieaye lllalaeoq slilggfrraa
 481 gvgsepgdqs gdenitqmlk rahdcrktae naakallmkl dgscggafav agcsvqpwes
 541 lssnshtstt sstasscdte ftkedeqrik dyiqqlkndr aavkltnlel esihidplsy
 601 dvkprgdsqr ldlenavlmq elmankeema elkaqlylle kekkalelkl streaqeqay
 661 lvhiehlkse vaeqkeqmr slsstssgsk dkggkecada aspalslael rttcsenela
 721 aeftnairre kklkarvqel vsalerlts seirhqqgae fyndlkrans nlvaayekak
 781 kkhgnklklk esqmmamver hetqvrmlkq rialleens rphtnetl

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FIG. 7E

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1  madvfpqnds  tasqdvsnrf  arkgalrqkn  vhevkdhkffl  arfkqptfc  shctdfiwgf
61  gkqgfqcqvc  cfvvhkrche  fvtfscpgad  kgpdtddprs  khkfkhtyg  sptfcdhcg
121  llyglihggm  kcdtdmnh  kqcvlnvpsl  cgmhtekrg  riykaevad  eklhvtvrda
181  knlipndpng  lsdpyvklkl  ipdpkneskq  ktktrstln  pqwnesftk  lkpsdkdrll
241  sveiwdwdrt  trndfngsls  fgvselmkmp  asgwykllng  eegeynvpi  pegdeegnme
301  lrqkfekakl  gpagnkvisp  sedrkapsnn  ldrvkltdfn  flmvlkgss  gkvmladrkg
361  teelyakkl  kkdvvigdd  vectmvekrv  lalldkppfl  tqlhscftv  drlyfvmeyv
421  nggdlnyhiq  qvgkfkepqa  vfyaaelsig  lfflhkrqii  yrdlklndvm  ldsoghikia
481  dfgmckehmm  dgttrtfcg  tpdyaieii  ayqpygksvd  wwaygvllye  mlagqppfdg
541  ededelqsi  mehnvsypks  lskeavslck  glmtkhpakr  lgcgpegerd  vrehaffiri
601  dweklenrei  qppfkpkvcg  kgaenfdkff  trggpvltp  dqlvianidq  sdfegfsyvn
661  pqfvhpiiq  ay

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FIG. 7F

1 mdiilceents leetnslmq lnddtrlysn dfnsgaents dafnwtvdse nrtnlscegc
 61 lpsclslh lqekwsall tavviltia gnllvinavs leklqnatn yflmslaiad
 121 mlglflvmpv smtilygyr wplpsklcav wylldvlfst asinhlcals ldryvaignp
 181 ihsrfrnrt kafkilaav tsvglsmpl pvfglqddsk vfkegscila ddnfvligsf
 241 vsffpleim vityfltiks lqeatlcvs dlgttraklas fsflpqesls seklfqrsh
 301 repgsytgrz tngsisneqk ackvlgivff lfvmwcpff itrinavick escedviga
 361 lnvfwigy lessavnlvy tlnktyrsa fsrylqcyk enkkplqlil vntipalayk
 421 seqlmgqkk nskqdakttd ndcsmvalgk qhseaskdn sdgvnekvag y

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FIG. 7G

1 malsyrvsēl qstipehiq stfwhvissn wsglqtesis eemqiveeq gnklhwaall
 61 ilmviptig gntlvllavs lekklqyath yflnelavad llvglfvmpi alltimfeam
 121 wplplvlcpa wlfldvlfst asimhlcais vdryiaikkp iqancynsra tafikltvw
 181 llsiglaipv plkgietdvd nnnitcvlt kerfgdmlf gslaafctpl aimivtyflt
 241 ihalqkkayl vknkppqrlt wltvstvfqr detpcsspek vamldgsrkd kalpnsqdet
 301 lmrstetigk ksvqtieneg raskvlgivf flflmwcpl fitniltvlc dscnqttlqm
 361 lleifwigy vssgvnplvy tlfnkttfrda fgryitcnyr acksvktlrk reskiyfrnp
 421 maenskffkk hginnginpa myqspmrirs stlqssii: ldtllltene gdkteeqvay
 481 Y

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FIG. 7H

1 maaasydqll kqvealknen snlrqeledn snhltklete asnmkevlkq lqgsiedean
 61 assgqldlle rikeinldss nfpvgklrsk msirsygere gsvssrsgec spvpngsfpr
 121 rgfvngsres tgyleeleke rsllladldk eeekedwyya qlqnltkrid slpltenfsl
 181 qtdmtrrrqle yearqirvam eeqlgtcqd m ekraqrriar iqglekdilr irqlqsgat
 241 eaerssqkxh etgshdaerg negqgvgein matesgnqgs ttrmdhetas vlssssthsa
 301 prrltshlgt kvemvyslls mlgtthdkddm srltlamess qdscismrqs gelpiliqll
 361 hgndkdsvll gnsrgskear arasaalhni ihsqpddkrg rreirvihll eqiraycetc
 421 wewqeahepg mdqdknmpa pvehqicpav cvlmklisfde ehrhamnelg qlqiaaellq
 481 vdcemygltn dhysitlrry agmaltnltf gdvankatl c smkgcmralv aqiksesedl
 541 qqviasvln lswradvnsk ktlrevgsvk almecalevk kestlksvls alwnlsahc
 601 enkadicavd galafivgtl tyrsqtnlia iiesgggilr nvssliatne dhrqilrenn
 661 clqtllqhlk shsltivsna cgtlwnlsar npkdqaalwd mgavsmklnl ihskhkmlam
 721 gsaaalrnlm anrpakykda ninspgsslp slhvrkqkal eaeldaqhls etfdnidnls
 781 pkashrskqr hkqsllygdyv fdtnrhddnr sdnfntgnmt vlspylnttv lpsssssrgs
 841 ldssrsekdr slerergigl gnyhpatenp gtsskrqgli sttaaqiakv meevsaihts
 901 qedrssgstt elhcvtdern alrrssaahh hsntynftks ensnrctcomp yakleykrss
 961 ndslnsvsss dgygkrgqmk psiesysedd eskfcsygyy padlahkhs anhmddndge
 1021 ldtpinyslk ysdeqlnsgr qspsqnerwa rpkhliledel kqsegrqsm qsttypvyte
 1081 stddkhlkfq phfgqgecvv pyrsrgangs etnrvgsnhg inqnvsgslc qeddyeddq
 1141 tnyserysse eqheeeerpt nysikyneek rhvdqpidys lkyatdipss qkqsfsfsks
 1201 ssgqskteh masssentst pssnakrqng lhpssagrs gqpqkaatck vssinqetiq
 1261 tycvedtpic frcsslssl ssaedeigcn qttqeadsan tlqlaeikek igtrsaedpv
 1321 sevpavsqhp rtkssrlqgs slssesarhk avefssgaks paksgaqtprk sppehyvqet
 1381 plmfarcstsv ssldsfesrs lassvqsepc sgmvgiisp sdldpspgqt mppsrsktpp
 1441 pppqtaqtpr evpknapta ekresgpkqa avnaavqrvg vlpdadtlh fatestpdgf
 1501 scssslsals ldepfiqkdv elrimppvge ndngnetese qpkesnenqe keaaktidse
 1561 kdlddsddd dieileeci sampkssrk akkpaqtast lpppvarkps qlpvylkps
 1621 qarlpqkxhv sftpgdmpv vycvegtpin fstatslsl tiesppnela agegvrqgaq
 1681 sgefekrdti ptegrstdea qgktsavti peldnkaee gdilaecins ampkghkhp
 1741 frvkkimdv qqasasssap nknqldgkk ktpspvkip qnteyrtvr knadsknnln
 1801 aervfsdnkd skkgnlkns kdfndklpnn edrvrgsfaf dsphhytpie gtpyofsrnd
 1861 slssldfddd dvdlrrekae lrkakenkes eakvtshtel tsnqgsankt qalakkpinr
 1921 gqpkpilqkq stfpqsskdi pdrgaatdek lqnfalientp vcfshnssls slsdidgenn
 1981 nkenepiket eppdsqgeps kpqasgyapk sfhvedtpvc fsrnssslsi sidseddllq
 2041 ecissampkk kkpserlkgdn ekhsprnmgg ilgedltldi kdiqrpdseh glspdsenfd
 2101 wkalgagans ivsslhqaaa aacslrqass dsdsilsiks glslgspfh tpdgeekpft
 2161 snkgprilkp gekstletkk ieseskgik gkkvykslit gkvrsnseis gmkqplqan
 2221 mpsisrgtm ihipgvnss sstspvskkg pplktpasks psegqtatts prgakpsvks
 2281 elspvarqts qiggsskaps rsgerdstps rpaqqplsrp igspgrnsis pgrngisppn
 2341 klsqprtsst petastkssg sgkmsytspg rqmsqqnlk qtgleknaas iprsesaskg
 2401 lnmangnga nkkvelsrms stksqgsesd rserpvlvrq stfikeapsp tlrrkleesa
 2461 sfeslpsrr pasptrsqaq tpvlspalpd mslsthasvq aggrwklppn leptieyndg
 2521 rpakrhdiar shsespsrlp inrsgtwkre hskhssslpr vstwrtrgss ssilsasses
 2581 sekaksdek hvnsisgtkq skengvsakg twrkikenef sptnstsqtv ssgatngaes
 2641 ktliygmapa vsktedvwr lddcpinnpr sgrsptgntp pvidsvseka npnikdskdn
 2701 qakqnvngs vpmrtvglen rlnsfigvda pdqkgteikp gqnpvpvse tnessivert
 2761 pfsssssskh sspsgtvaar vtpfnynpss rkssadstsa rpsqiptpvn nntkkrdkt
 2821 dstessgtqs pkrhsqsyly tsv

FIG. 8

p75NGFR

(Low-affinity nerve growth factor receptor)

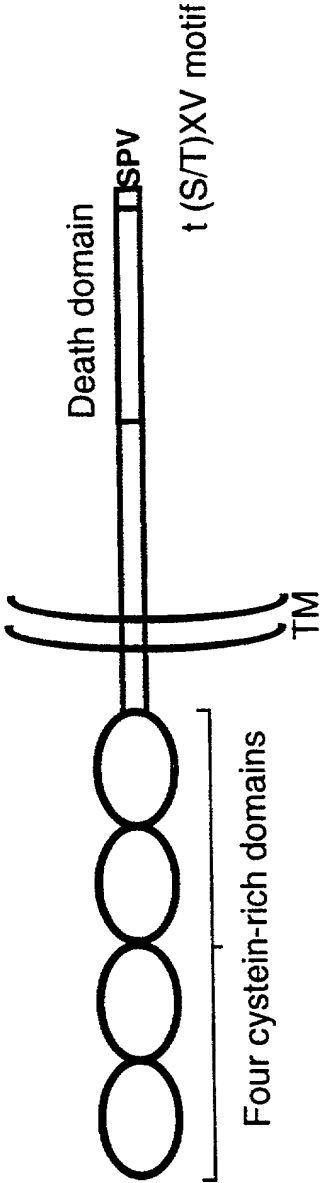
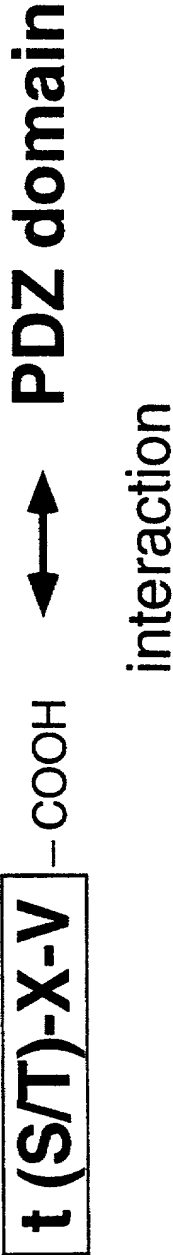


FIG. 9

	C-terminal amino acid sequence
Fas	NEIQSLV
p75NGFR	STATSPV



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FIG. 10
In vitro interaction of ³⁵S-labeled FAP-1 with various receptors
— FAP-1 binds to the cytoplasmic region of p75NGFR. —

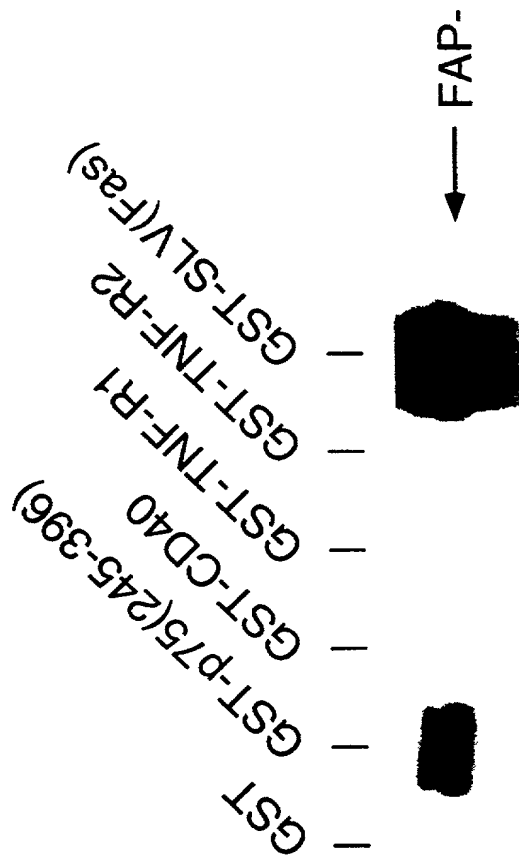


FIG. 11A
FAP-1 binds to C-terminal three amino acids SPV of p75NGFR.

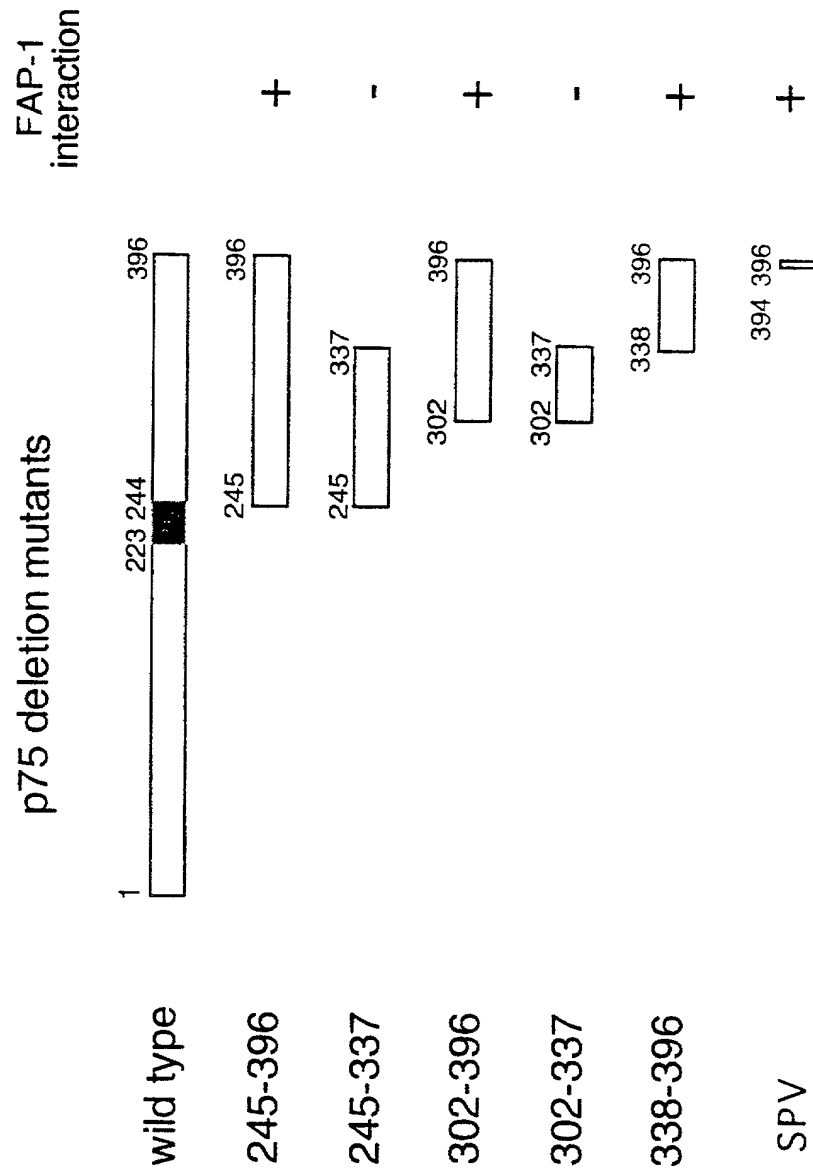


FIG. 11B

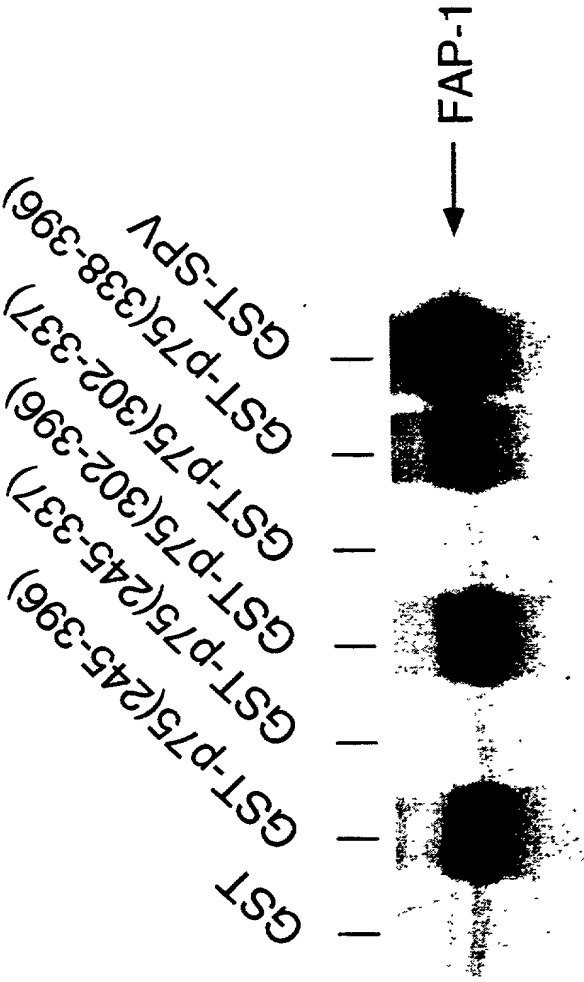


FIG. 12
FAP-1 binds to p75NGFR C-terminal cytoplasmic region in yeast.

	VP16-FAP-1	VP16-cRaf
LexA-p75NGFR(338-396)	+	-
LexA-p75NGFR(365-396)	+	-
LexA-Fas	++	-
LexA-Ras ^{V12}	-	+
LexA-Lamin	-	-

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below:

<u>Provisional Application No.</u>	<u>Filing Date</u>	<u>Status</u>
N/A		

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States Application(s), or Section 365(c) of any PCT International Application(s) designating the United States listed below. Insofar as this application discloses and claims subject matter in addition to that disclosed in any such prior Application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56, which became available between the filing date(s) of such prior Application(s) and the national or PCT international filing date of this application:

<u>Application Serial No.</u>	<u>Filing Date</u>	<u>Status</u>
PCT/US97/12677	July 18, 1997	Pending
08/681,219	July 22, 1996	Pending

And I hereby appoint

John P. White (Reg. No. 28,678); Christopher C. Dunham (Reg. No. 22,031); Norman H. Zivin (Reg. No. 25,385); Jay H. Maioli (Reg. No. 27,213); William E. Pelton (Reg. No. 25,702); Robert D. Katz (Reg. No. 30,141); Peter J. Phillips (Reg. No. 29,691); Wendy E. Miller (Reg. No. 35,615); Richard S. Milner (Reg. No. 33,970); Albert Wai-Kit Chan (Reg. No. 36,479); Robert T. Maldonado (Reg. No. 38,232); Paul Teng (40,837); George M. MacDonald (Reg. No. 39,284); Richard F. Jaworski (Reg. No. 33,515); Elizabeth M. Wieckowski (Reg. No. 42,226); Pedro C. Fernandez (Reg. No. 41,741); and Gary J. Gershtik (Reg. No. 39,992).

and each of them, all c/o Cooper & Dunham LLP, 1185 Avenue of the Americas, New York, New York 10036, my attorneys, each with full power of substitution and revocation, to prosecute this application, to make alterations and amendments therein, to receive the patent, to transact all business in the Patent and Trademark Office connected therewith and to file any International Applications which are based thereon under the provisions of the Patent Cooperation Treaty.

Please address all communications, and direct all telephone calls, regarding this application to:

John P. White

Reg. No. 28,678

Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
Tel. (212) 278-0400

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or

first joint inventor Taka-Aki Sato

Inventor's signature

Taka-Aki Sato

Citizenship Japan

Date of signature

2/5/99

Residence 1275 15th Street, Apt. 8P, Fort Lee, New Jersey 07024

Post Office Address same as above

Full name of joint

inventor (if any) Junn Yanagisawa

Inventor's signature

Citizenship Japan

Date of signature

Residence 3-12-6 Sakura-gaoka, Tama-City, Tokyo 206 Japan

Post Office Address same as above

Full name of joint

inventor (if any)

Inventor's signature

Citizenship

Date of signature

Residence

Post Office Address

Please address all communications, and direct all telephone calls, regarding this application to:

John P. White _____ Reg. No. 28,678

Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
Tel. (212) 278-0400

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Full name of sole or

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Inventor's signature

Citizenship Japan

Date of signature

Residence 1275 15th Street, Apt. 8P, Fort Lee, New Jersey 07024

Post Office Address same as above

Full name of joint

inventor (if any) Junn Yanagisawa

Inventor's signature

Citizenship Japan

Date of signature

1999 Feb 10

Residence 3-12-6 Sakura-gaoka, Tama-City, Tokyo 206 Japan

JPX

Post Office Address same as above

Full name of joint

inventor (if any)

Inventor's signature

Citizenship

Date of signature

Residence

Post Office Address